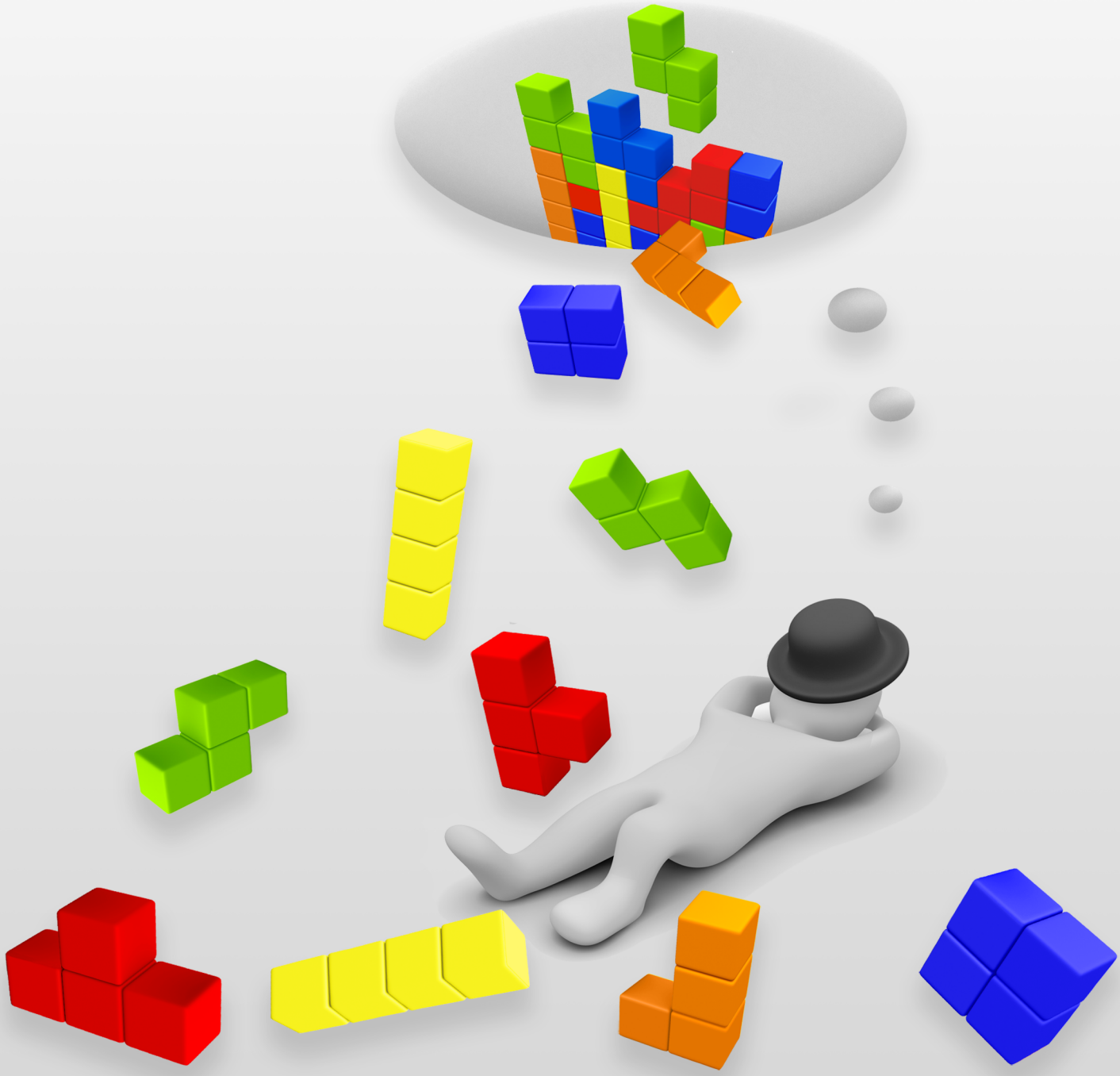
Caroline Kussé

# Functional interactions between memory processes and spontaneous brain activity

## Behavioral, EEG and fMRI studies



PhD thesis submitted to the University of Liège
in partial fulfillment of the requirements for the degree of
doctor in biomedical and pharmaceutical sciences

Cyclotron Research Center

University of Liège

Belgium

# FUNCTIONAL INTERACTIONS BETWEEN MEMORY PROCESSES AND SPONTANEOUS BRAIN ACTIVITY

## BEHAVIORAL, EEG AND FMRI STUDIES

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Promotor: Pierre Maquet

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# ABSTRACT

Episodic memories pertain to specific events for which both content and context can be consciously recalled and verbalized. Between encoding and retrieval, episodic memories are thought to be maintained within hippocampal and neocortical circuits, then to be gradually consolidated into robust memories which can eventually be accurately and comprehensively retrieved in the long term. However, the mechanisms by which a recent episodic memory is initially maintained in the brain are not yet fully understood.

The main aim of this thesis is to examine whether learning an engaging task modifies spontaneous brain activity during subsequent resting state wakefulness and sleep onset, and whether such replay of brain activity has an effect on offline memory processing. We examined healthy human volunteers behaviorally and with non-invasive neuroimaging techniques in two different studies.

In the first study, we examined the emergence of task-related hypnagogic hallucinations during a daytime nap with EEG. In the experimental group (n=16), participants played Tetris in the morning for two hours during three consecutive days, while in a first control group (n=13, controlling the effect of experience), participants did not play any game, and in a second control group (n=14, controlling the effect of anticipation), participants played Tetris after the nap. During afternoon naps, participants were repetitively awakened during sleep stage 1 and were asked to report their mental content. Reports content was scored by three judges (inter-rater reliability 85%). In the experimental group, 48 out of 485 (10%) sleep-onset reports were Tetris-related. These reports mostly consisted of images and sounds with very little emotional content. They exactly reproduced Tetris elements or mixed them with other mnemonic components. By contrast, in the first control group only 1 report out of 107 was scored as Tetris-related (1%), and in the second control group only 3 reports out of 112 (3%) (between groups comparison; p=0.006). Hypnagogic hallucinations were more consistently induced

by experience than by anticipation (p=0.039) and they were predominantly observed during the transition of wakefulness to sleep. The observed attributes of experience-related hypnagogic hallucinations are consistent with the particular organization of regional brain activity at sleep onset, characterized by high activity in sensory cortices and in the default mode network.

In the second study, we tested if brain activity generated during learning is spontaneously repeated during subsequent resting wakefulness. Healthy participants (n=11) were scanned in a randomized within-subject cross-over design composed of two conditions in which fMRI rest sessions flanked an active fMRI session. We applied machine learning based multivariate pattern analysis on these fMRI time series to calculate the percentages of task-related scans before and after a memory task (encoding a two dimensional trajectory of face, building and animal pictures) and before and after a control task (an auditory oddball). Activity patterns elicited by visual stimuli were spontaneously expressed in the visual ventral stream before any cognitive challenge. We found that 1.11% more scans were task-related after learning than before, and that the larger the difference between the proportions of spontaneous brain activity linked to a task before and after this task, the better the memorization of task features by the subject, suggesting that reactivations during post-task rest are linked to the memorization of the task. On the other hand, 0.26% less scans were related to the memory task after a control task than before, suggesting that the control task had a repressive effect on the scans related to the memory task. Memory encoding modulated the temporal organization of the spontaneous activity in episodes of longer duration (4 to 6 seconds). Our results show that human memories are maintained during resting wakefulness by temporally organized repetitions of regional brain activity. However, because our other analyses (dynamic causal modeling, cross-correlations and explained variance, and spatial networks based on independent component analysis) could not confirm these findings, we suggest that fMRI might not be the most appropriate methodology to further characterize memory consolidation directly.

Our results add to the growing body of evidence suggesting that offline processing of explicit memories occurs during wakefulness. They extend our understanding of human spontaneous brain activity and its relationship to offline memory processing, although more research is warranted to further explore the details of the memory consolidation process. Interesting perspectives would be to pursue this work during sleep or with other neuroimaging methods such as high density EEG or simultaneous fMRI and EEG.

# ACKNOWLEDGEMENTS

Doing a PhD means a huge amount of work. It's not only about collecting data, interpreting results and writing articles, but also about learning how to manage your time, deal with deadlines, working in a team, and maybe most of all it is about personal growth. Of course I couldn't do all this by myself. Many helpful and interesting people have crossed my path during the last five years and I would like to express my thanks to them in this (far too short) chapter of my thesis.

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I love computers… if they work properly. However, computers have the nasty habit of crashing at crucial moments, for example while examining a volunteer in the

MRI scanner or when a complex Matlab analysis is running for weeks. Thanks also to the lab IT specialist Christian Degueldre for sorting out such computer issues.

When I arrived at the lab a few years ago, I barely knew the name of that powerful program Matlab. That I'm now able to write code for an experiment and its complete analysis from scratch and that I'm starting to understand some of the mysteries of the SPM toolbox, is thanks to Pierre Maquet, Christophe Phillips, and certainly Karel Crombecq and Jessica Schrouff who both very patiently answered all my questions and taught me how to code more efficiently. Also Peter Temmerman, although not a Matlab specialist, helped me a lot with understanding more about programming. I'm neither a programmer nor an engineer and never will be, but thanks to you I can now create and manage my own scripts that are working, although not always very beautifully coded.

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Driesen: mama, thank you for just being there when I needed a listening ear and helping with too many things to list, such as translations, valuable feedback on proofreading my manuscripts, babysitting, and keeping me up-to-date with what happens on planet Earth. I also would like to thank my sensei, Danny Celis, for teaching me to have the strength to never give up.

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Caroline

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## Acronyms

| | |
|---|---|
| A | animals |
| AA | animal area |
| AUD | auditory network |
| B | buildings |
| BOLD | blood oxygen level dependent |
| BW | bandwidth |
| CNR | contrast-to-noise ratio |
| CORSICA | correction of structured noise using spatial independent component analysis |
| CSF | cerebro-spinal fluid |
| CV | cross-validation |
| dATT | dorsal attentional network |
| DCM | dynamic causal modeling |
| DD | daydreaming |
| df | degrees of freedom |
| DM | default mode network |
| ECOC | error-correcting output code |
| ECoG | electrocorticography |
| EEG | electroencephalography |
| EMG | electromyography |
| EOG | electrooculography |
| EPI | echo-planar imaging |
| EV | explained variance |
| F | faces |
| FA | flip angle |
| FASST | fMRI artefact rejection and sleep scoring toolbox |
| FFA | fusiform face area |
| FFX | fixed effects analysis |
| fMRI | functional magnetic resonance imaging |
| FoV | field of view |
| FTT | finger tapping task |
| FWE | family-wise error |
| FWHM | full width at half maximum |
| GLM | general linear model |
| GP | Gaussian processes |
| HRF | hemodynamic response function |
| Hz | Hertz |
| IC(A) | independent component (analysis) |
| IDPC | integrated difference in partial correlation |
| IID | independent and identically distributed |
| IPI | imaginal process inventory |

| | |
|---|---|
| KSS | Karolinska sleepiness scale |
| L | distance |
| LSD | post hoc least significant differences |
| LSDQ | London sleep and dream questionnaire |
| LTP | long-term potentiation |
| max | maximum |
| MDEFT | modified driven equilibrium Fourier transform |
| med | median |
| MEG | magnetoencephalography |
| min | minimum |
| mm | millimeter |
| MNI | Montreal neurological institute |
| MOT | sensorimotor network |
| ms | millisecond |
| MVPA | multi-variate pattern analysis |
| μs | microsecond |
| N | number of included subjects |
| NEDICA | network detection using ICA |
| NOI(s) | network(s) of interest |
| NREM | non-rapid eye movement |
| NS | non significant |
| PET | positron emission tomography |
| PPA | parahippocampal place area |
| Pr | proportion |
| PSG | polysomnography |
| PSQI | Pittsburgh sleep quality index |
| PVT | psychomotor vigilance task |
| px | pixel, picture element in a 2D image |
| REM | rapid eye movement |
| RFA | recursive feature addition |
| RFX | random effects analysis |
| RM-ANOVA | repeated measures analysis of variance |
| ROI(s) | region(s) of interest |
| RSC | retrosplenial cortex |
| s | second |
| S1 | sleep stage 1 |
| S2 | sleep stage 2 |
| S3 | sleep stage 3 |
| S4 | sleep stage 4 |
| SD | standard deviation |
| SEM | slow eye movement |
| SMP | sleep midpoint |
| SNR | signal-to-noise ratio |

| | |
|---|---|
| SPM | statistical parametric mapping |
| SRTT | serial reaction time task |
| SVM | support vector machines |
| TA | acquisition time |
| TE | echo time |
| TI | inversion time |
| TR | repetition time |
| vATT | ventral attentional network |
| VIS | visual network |
| VOI(s) | voxel(s) of interest |
| vx | voxel, volume element in a 3D image |
| W | wakefulness |
| y | year |

# 1. INTRODUCTION

This chapter is based on:

- Shaffii-Le Bourdiec A, Muto V, Mascetti L, Foret A, Matarazzo L, *Kussé C*, Maquet P (2010) Contribution of sleep to memory consolidation. Future Neurology 5(2): 325-338.

- *Kussé C*, Shaffii-Le Bourdiec A, Schrouff J, Matarazzo L, Maquet P (2012) Experience-dependent induction of hypnagogic images during daytime naps: a combined behavioural and EEG study. J Sleep Res 21(1): 10-20.

- Schrouff* J, *Kussé* C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding semi-constrained brain activity from FMRI using support vector machines and gaussian processes. PLoS One 7(4): e35860.

- Schrouff J, *Kussé C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding spontaneous brain activity from fMRI using gaussian processes: tracking brain reactivation. In: PRNI, London, doi 10.1109/PRNI.2012.19.

- Schrouff* J, *Kussé* C*, Wehenkel L, Luxen A, Maquet P, Phillips C (Submitted) Temporally structured memory replay during resting wakefulness in humans.

This thesis work covers spontaneous brain activity during different vigilance stages in healthy humans, examined behaviorally and with macroscopic neuroimaging techniques such as EEG and fMRI. I was particularly interested in memory processes during wakefulness and sleep and their potential behavioral (conscious) and neural correlates. How does the human brain process information related to past experiences?

In a first study, I assessed the learning-dependency of hypnagogic hallucinations, a curious dream-like phenomenon occurring at the onset of sleep. In particular, we examined behaviorally whether an engaging task (playing the computer game Tetris) would be able to elicit task-related hypnagogic hallucinations during a daytime nap, while brain activity was continuously monitored with EEG. Although hypnagogic hallucinations are an omnipresent phenomenon, their origin and function remain very poorly understood.

In a second study, I aimed at characterizing the neural correlates of memory maintenance during post-learning resting state wakefulness. Brain activity of volunteers was measured with fMRI while they were learning a trajectory of pictures (of human faces, buildings and animals) and during pre- and post-learning rest sessions. Data was analyzed using several techniques, namely dynamic causal modeling, explained variance, identification of spatial networks using independent component analysis, and multivariate decoding which is based on multivoxel pattern analysis. We examined also whether a higher amount of task-related replay would be correlated with better memory performance afterwards.

Both experiments require a theoretical introduction about several topics, which will be dealt with in the following sections:

- Spontaneous brain activity during different vigilance states and its role in memory consolidation; stages and consciousness in the sleep wake/cycle. Spontaneous brain activity is the red line through this thesis: both studies assess the purpose of spontaneous brain activity.

Moreover, an important aspect of the first study is to detect the exact vigilance stage in which hypnagogic hallucinations occur.

- Various forms of conscious and spontaneous mentation during wakefulness and sleep in order to set the context of the first experiment. In this study, it is important to differentiate correctly between hypnagogic hallucinations and e.g. mental imagery and dreams. In the introduction, the behavioral (subjective) differences will be described, while a more detailed description of the characteristics on EEG recordings (objective) can be found in the material and methods chapter of the considered study.

- Different memory systems, an overview of the crucial steps in memory maintenance (encoding, consolidation and retrieval) and replay mechanisms underlying memory consolidation. This section is necessary as the novelty of the second experiment is to characterize memory consolidation directly, without confounding influences of retrieval.

- Functional brain specialization and integration. Because the second study is crucially based on the characteristic specialization of visual areas, we summarize the most well-known category-specific visual brain areas and different theories about processing strategies: are these regions really important in processing one category of stimuli, or do they represent levels of expertise?

An explanation of the neuroimaging techniques (EEG and fMRI) and analyzing methods (scoring of the naps for the first study; dynamical causal modeling, explained variance, spatial networks and multivariate decoding for the second study) can be found in the material and methods section of each research chapter.

## 1.1. Spontaneous brain activity

The first part of the introduction deals with spontaneous brain activity during different vigilance states and its role in memory consolidation. Spontaneous brain activity is the main theme of this thesis.

The classic view of brain functioning posits that the brain is mainly reflexive, driven by environmental demands and external stimuli in order to interpret incoming information and program motor output (Raichle, 2006). However, recent *neuroimaging* results suggest that the majority of brain activity is intrinsic, spontaneous, and involved in maintaining information for interpretation, responding to, and even predicting environmental demands.

*Functional neuroimaging* techniques allow in vivo measurements of an aspect of brain function, often to understand the relationship between activity in certain brain areas and specific mental functions. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) measure hemodynamic changes induced by regional changes in neuronal activity with high spatial resolution (i.e. a few millimeters). Electroencephalography (EEG) and magnetoencephalography (MEG) measure respectively the neuronal electrical or magnetic activity with high temporal resolution (i.e. milliseconds).

Indeed, even in the absence of sensory input neuronal networks remain very active, as already shown by many functional studies searching for a baseline brain activity (Gusnard and Raichle, 2001; Raichle and Mintun, 2006; Fox and Raichle, 2007; Fox et al, 2007; Boly et al, 2008). Moreover, cost-based analyses suggest spontaneous intrinsic activity is an important aspect of normal brain functioning, far more significant than evoked activity in terms of overall brain function (Raichle, 2006; Raichle and Mintun, 2006).

In humans, this spontaneous brain activity is expressed as a variety of rhythms on electroencephalographic recordings (Buzsaki and Draguhn, 2004) and intrinsic fluctuations of the functional magnetic resonance imaging signal (Fox and Raichle, 2007).

**Role in memory consolidation**

Although the exact purpose of spontaneous brain activity is still largely unknown, it is thought to underlay intertrial variability (Arieli et al, 1996), modulate behavior (Fox et al, 2007), perception (Boly et al, 2007), consciousness (Fox et al, 2006) and memory consolidation (Wagner et al, 1998; Tsodyks et al, 1999; Kenet et al, 2003). It is often assumed that this spontaneous activity is related to the treatment of several types of information: personal thoughts, memories, emotions, intentions, etc. Indeed, even in the absence of external input, the brain is capable of generating representations or images, as occurs in dreams and hallucinations (Llinás, 2001; Hobson, 2002). Furthermore, spontaneous thoughts during wakefulness are an omnipresent phenomenon, occupying as much as one third

of our waking time, which underlines the importance of the spontaneous activity of the brain (Christoff et al, 2011).

Evidence exists that relates spontaneous brain activity to consolidation of memory traces. For example, during sleep following a spatial learning, firing sequences have been observed that are similar to encoding sequences in hippocampal neuronal populations (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Hirase et al, 2001; Louie and Wilson, 2001; Lee and Wilson, 2002; Ji and Wilson, 2007; Peyrache et al, 2009) and in the cortex (Qin et al, 1997; Euston et al, 2007; Peyrache et al, 2009; Eagleman and Dragoi, 2012; Mohajerani et al, 2013). It seems that these reactivations are not strictly limited to sleep, as similar modifications of neocortical activity have been registered during resting state wakefulness (Hoffman and McNaughton, 2002; Eagleman and Dragoi, 2012; Mohajerani et al, 2013).

## 1.2. Mentation

Intrinsic or spontaneous brain activity is sometimes reflected in spontaneous mentation. Depending on the state of consciousness, many types of spontaneous mental activity can be observed such as thoughts, intentions, memories, emotions, illusions, dreams and hypnagogic hallucinations. To clarify the object of the present work, we explain operational definitions in this chapter. As there is no consensus on the definition of dreams, for instance, the aim is only to set the stage for this particular study. Mental imagery, *hypnagogia* and dreams are subjective experiences, while the wake state, sleep stage 1, and rapid eye movement sleep (REM sleep) in which they can occur respectively, are physiologically defined states of consciousness. Therefore, the subjective experiences will be defined by their psychological features and the states of consciousness will be defined by their objective physiological characteristics in 3.2.4.2.

*Hypnagogia* (Maury, 1848) is derived from the Greek word hypnos, which means sleep, and agogos, which means introducing or leading to. Please note that sometimes the term hypnagogia is used in a more general sense to describe both hypnagogic and hypnopompic hallucinations , occurring at the onset to and awakening from sleep, respectively, as the experience of both types of hypnagogia is largely the same (Ellis, 1897). However, in this thesis the term hypnagogia will be used only to describe the experiences occurring while drifting off to sleep, as originally meant (Maury, 1848; Myers, 1892).

### 1.2.1. Mental imagery

Imagery is a subjective phenomenon, including mental representations that are mostly visual or auditory of modality. Imagery, whether voluntary (e.g. mental imagery) or involuntary (e.g. hypnagogic imagery), resembles the inner experience of perceiving something that is not present to the senses (McKellar, 1957). Mental imagery is assumed to play a role in memory, thinking and motivation, as imagery experiences are often understood as echoes or reconstructions of past actual perceptual experiences.

*Differences between hallucinations and other perceptions* (Chiu, 1989):
- Dreams occur during REM sleep and contain a story-like plot in which the dreamer is involved as an actor.
- Illusions involve distorted or misinterpreted real perception.
- Mental imagery does not mimic real perception and is under voluntary control.
- Pseudohallucinations do not mimic real perception but are not under voluntary control.

### 1.2.2. Dreams

Dreams are mental representations occurring while one is sound asleep, especially during REM sleep (Dement and Kleitman, 1957b) which is also called paradoxical sleep (Jouvet et al, 1959a, 1959b, 1959c), as brain activity during this sleep stage resembles awake activity. Dream content is vivid and very much story-like, often with the dreamer as actor. Complex objects (people, buildings, etc.) and rapidly changing series of images, sounds and feelings (especially fear, elation and anger, more than sadness, shame and guilt) play an important role in the plot, which has often a high degree of bizarreness or improbability of time, place, person and actions and lacks orientation stability (Hobson et al, 1987; Hobson, 1988), although it is experienced as waking reality. The sensory modalities accounting for the major part of dreams are visual and motor (Hobson, 1988; Zadra et al, 1998). Memory for even very vivid dreams is evanescent and tends to fade quickly upon awakening (Hobson et al, 2003).

### 1.2.3. Hypnagogic hallucinations

Hallucinations in general are involuntary false sensory perceptions in the absence of an actual external stimulus. They occur concurrently with actual observations in a conscious and awake or somnolent state (i.e. excluding dreams), and have qualities of real sensations such as vividness, substantiality, and location in external objective space (Mullen, 1979). Hallucinations can occur in any sensory modality. Hallucinations can occur in a variety of

different situations: auras preceding migraine attacks or epilepsy, psychosis in paranoid schizophrenia (e.g. hearing voices), drug induced hallucinations, delirium tremens, sensory deprivation, or in more common conditions like after seeing a bright flickering light, sleep deprivation, or while waking up or falling asleep (James, 1890). For our study, we are interested in the latter category which will be described in more detail in this chapter.

Hypnopompic hallucinations (Myers, 1892, 1903) occur while waking up from sleep.

Hypnagogic hallucinations, our main interest, occur while falling asleep and are usually described as short visual percepts like faces, landscapes, and natural or social scenes, sometimes related to previous daytime experience. They are usually without narrative content and almost never contain a story-like plot, although some very short and simple exceptions may occur. Specific sensations such as floating, visions of flashing light, out of body experiences, numbness of the legs and changes in perceived body size and proportions are frequently reported (Mavromatis, 1987). These percepts may be of pseudohallucinatory (i.e. with preserved insight of unreality) or truly hallucinatory character (i.e. experienced as if real). Hypnagogic images are an isolated appearance in the air, appearing to be located just a few inches away at reading distance from the eye, but not surrounded by a complete imaginary world (Sartre, 1940; Siegel, 1977). As soon as they are attentively focused on or tried to be consciously controlled, they disappear immediately (Maury, 1865). Hypnagogic hallucinations are a common phenomenon occurring in the whole population (Richardson et al, 1981; Ohayon et al, 1996; Ohayon, 2000).

Although hypnagogic states are highly variable with large individual differences (Rechtschaffen, 1994), they have unique behavioral, electrophysiological and subjective characteristics which have been examined with inventive techniques. These topics will be dealt with in the following paragraphs.

*Synonyms of hypnagogic hallucinations* are sleep-onset mentation, presomnal or anthypnic sensations, visions of half-sleep, oneirogogic images, the borderland of sleep, praedormitorium (Mavromatis, 1987), half-dream state, predream condition, sleep onset dreams, dreamlets (Schacter, 1976), wakefulness-sleep transition state (Bodizs et al, 2005; Bodizs et al, 2008).

### 1.2.3.1. Behavioral correlates

*Reality testing* is the capacity to distinguish what is occurring in one's own mind from what is occurring in the external world.

Behavioral correlates of hypnagogic hallucinations are sparse. Typical are a decreased awareness of observing one's mental content and loss of volitional control over mentation, inaccurate time perception, reduced awareness of the environment, and reduced *reality testing* (Foulkes and Vogel, 1965; Mavromatis and Richardson, 1984; Rechtschaffen, 1994).

*Hypnic jerks*, also called sleep starts or sleep twitches, are involuntary muscle twitches in various skeletal muscles, predominantly in the limbs, which occur when falling asleep. They may cause arousal.

*Hypnic jerks* in arms or leg muscles can be associated with vivid kinesthetic hallucinations or illusionary body movements. The muscle twitch may for example resemble the startle reflex when experiencing a falling sensation (Nielsen, 1992; Germain and Nielsen, 2001; Askenasy, 2003).

Another feature includes the hypnagogic/hypnopompic speech phenomenon, which occurs when a person hears himself uttering words, often nonsensical or irrelevant, just as they are falling asleep or waking from sleep (McKellar, 1989).

### 1.2.3.2. Electrophysiological correlates

EEG recordings can be used to reliably detect the state in which hypnagogic images can occur (Hori, 1985; Hori et al, 1994; Germain and Nielsen, 1997; Vaitl et al, 2005): they occur in a state of somnolence, more precisely sleep stage 1. In this stage, the low voltage EEG pattern shows a fragmentation and a progressive disappearance of alpha rhythm (Davis et al, 1937; Foulkes and Vogel, 1965; Foulkes and Schmidt, 1983) and an appearance of theta rhythm. EOG recordings show slow, rolling eye movements, mainly in the horizontal direction, and the EMG is characterized by a diminished muscle relaxation, sometimes with hypnic jerks.

Nine detailed stages of sleep onset have been described to identify more precisely the EEG state which accompanies hypnagogic imagery, according to the proportion of alpha rhythm (stages 1-3), suppression of low amplitude waves less than 20 μV or EEG flattening (stage 4), theta ripples (stage 5) proportions of vertex sharp waves (stages 6 and 7)

and presence of spindles (stages 8 and 9), and also the amount of hypnagogic images occurring in each of the stages (Hori et al, 1994). These findings were supported by others, who found that spontaneous hypnagogic imagery occurred mostly during Hori's stage 4 and 5, respectively EEG flattening and theta ripples (Germain and Nielsen, 1997). Early research already showed that in sleep stage 2 the occurrence of hypnagogic hallucinations decreases dramatically, although in these days it was not yet called stage 2 (Davis et al, 1937).

An association between short flashes of dreamlike imagery and drop-offs in alpha EEG activity has been observed (Davis et al, 1937). Flattened or decelerated alpha and/or slow theta EEG activity are mostly associated with nonemotional visual and auditory impressions of varying complexity, mostly experienced as unreal (Kuhlo and Lehmann, 1964).

Prominent theta activity appears to be associated with a cognition pattern consisting of mainly visual (Germain and Nielsen, 1997) and emotional experiences of good recall quality with low body perception and orientation, whereas slower frequencies are associated with lower recall quality (Lehmann et al, 1995). EEG source localization techniques revealed that abstract thoughts are generally associated with more anterior and deeper sources than those of visual imagery, particularly in the delta/theta band (Lehmann et al, 1993).

Unimodal visual and kinesthetic images (apparent self-movements) are characterized by decreases in all frequency bands except delta, which increases. Kinesthetic hallucinations are accompanied by prefrontal and frontal delta activation, and visual by delta activation in more left-central and temporal regions. The documented spread of anterior to posterior delta power may be associated with sense-specific imagery processes (Germain and Nielsen, 2001).

Alpha and beta frequency bands appear to be associated with predominantly acoustic experiences, the subjects uninvolved in the narrative, while visual and tactile modes

are almost absent (Lehmann et al, 1995). These hallucinations are void of emotional connotations but with high body perception, orientation and vigilance.

Auditory thresholds to elicit a response from the subject during stage 1 sleep are much lower than in REM sleep (Davis et al, 1939). On EEG recordings, an elevated response to sounds can be observed at sleep onset (Ornitz et al, 1967), paralleling the high receptiveness for suggestion during stage 1 and ready incorporation of external stimuli into hypnagogic hallucinations (Hollingworth, 1911).

As for physiological correlates, hypnic jerks or other bodily sensations often are accompanied in the EEG by a vertex sharp wave or small K-complex (Vaitl et al, 2005), corresponding to Hori's EEG stages 8 and 9 (Hori et al, 1994), an electrical event which is commonly attributed to an arousal. They can be due to a temporary re-excitation of some part of the reticular formation of the brain stem, while the associated hypnagogic hallucinations could then be due to arousal in some other part of this system (Anonymous, 1959; Oswald, 1959). Sleep paralysis on the other hand, may be attributed to a delayed arousal in some part of the same system.

Changes in abdominal-thoracic respiratory patterns have also been noted with progressive loss of wakefulness (Timmons et al, 1972): abdominal-dominant breathing was associated with relaxed wakefulness, abdominal-thoracic equality with drowsiness, and thoracic-dominant breathing with sleep onset. During drowsiness, variations in amplitude of abdominal movements were closely related to vacillations between alpha and theta activity in the EEG. In addition, a low level of frontalis muscle activity may be related to sleep onset (Budzynski, 1972; Stoyva, 1973).

### 1.2.3.3. Subjective perceptions

**Sensory modalities**

Although hypnagogic hallucinations can occur in any sensory modality, visual imagery seems to occur most frequently, followed by auditory and tactile-kinesthetic perceptions (Maury, 1865; Foulkes and Vogel, 1965; Green et al, 1970; Schacter, 1976). Just as in waking, different sensory modalities can be engaged in the same event (sometimes *synesthetic* hallucinations are reported), and can range from very clear and concrete hallucinations to vague and barely perceptible imagery which is difficult to describe precisely (Mavromatis, 1987).

The best researched hypnagogic phenomena are those of the visual modality. In general, they are characterized by externality, autonomy, brevity of duration, sometimes clarity of detail and vividness of color or sometimes not at all, internality, and the sense of reality. One of the visual features of hypnagogic hallucinations are *phosphenes* (Nicholson, 1996). They are typically fleeting and changing very rapidly.

Auditory hypnagogic hallucinations occur also frequently. They can vary in intensity from faint impressions to loud noises, such as a bomb explosion or a clash of cymbals (such as *exploding head syndrome*). Common experiences are hearing a telephone ringing, neologisms, irrelevant sentences containing unrecognizable names or nonsense words, meaningful responses to one's thought of the moment, someone calling their own name, or a music tune or poem (Mavromatis, 1987).

Common examples of kinesthetic and proprioceptive experiences are numbness and changes in perceived body size and proportions (e.g. swelling of one of the limbs), as well as tactile sensations such as *paresthesia* and *formication*. Vestibulo-motor hallucinations of floating, flying, falling, bobbing, illusory movements and out of body experiences are also commonly reported (Mavromatis, 1987).

*Synesthesia* is a phenomenon in which stimulation in one sensory modality induces an experience in another sensory modality, e.g. associating music with colors.

*Phosphenes* are the experience of seeing light without light actually entering the eye. They are perceived as flashes of light, random speckles, lines or geometrical patterns, still or moving, monochromatic or richly colored.

*Exploding head syndrome*, also known as auditory sleep starts, is a parasomnia in which the patient experiences a loud bang in the head that seems to originate from inside the head, although it is usually not accompanied by pain.

*Paresthesia* is a sensation of tingling, pricking or burning with no physical effect. Common examples are pins and needles, a limb falling asleep, or *formication* (insects crawling on the skin).

Although gustatory, olfactory and thermal sensations have all been reported (e.g. a sense of heat or cold coursing through the body), these modalities are less frequently experienced (Mavromatis, 1987).

**Cognitive processes**

Emotions are also a common characteristic of hypnagogic hallucinations and range from euphoria and bliss to fear and nightmarish, frightening experiences (Cheyne, 2000; Revonsuo, 2003).

Cognitive processes in hypnagogia differ from those of other states of consciousness, characterized by openness, receptivity and susceptibility to suggestion (Ellis, 1897; Schacter, 1976), readiness to incorporate external and internal stimuli into hypnagogic mentation (Hollingworth, 1911), internalization of the physical and mental environment, and an illogic and fluid association of ideas (Mavromatis, 1987). Anticipatory warning experiences, *insight and problem-solving* phenomena have been reported.

Many inventors, artists and scientists have reported moments of *enhanced creativity or insight* into a problem during hypnagogic hallucinations (Barrett, 2001), such as chemist August Kekulé (Figure 1), inventor Thomas Edison, painter Salvador Dalí (Figure 3), composers Beethoven and Richard Wagner, scientists Nikola Tesla and Isaac Newton.

It has been suggested that hypnagogia and REM sleep are involved in semantic memory consolidation (Stickgold, 1998; Stickgold and Walker, 2005) although this has been disputed (Vertes and Eastman, 2003). Hypnagogic hallucinations are often replaying previous waking experiences from that day or from older related memories (Stickgold et al, 2001b). Recent experimental evidence exists of seeing falling blocks after Tetris gaming (Stickgold et al, 2000) and skiing experiences after playing Alpine Racer (Emberger, 2001; Stickgold et al, 2001a; Wamsley et al, 2010).

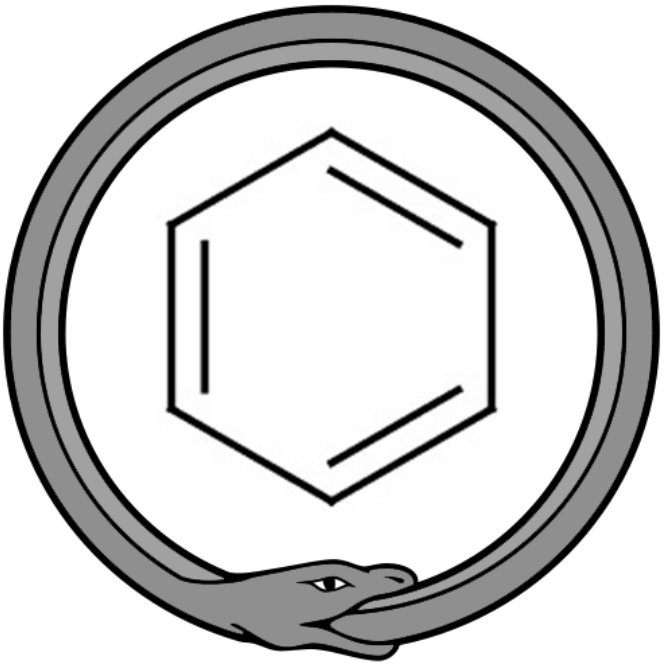

Figure 1. Chemist August Kekulé discovered the cyclic structure of benzene in 1865, a milestone in chemistry history, in a hypnagogic hallucination of an ouroboros (a snake swallowing its own tail): *"...I was sitting writing on my textbook, but the work did not progress; my thoughts were elsewhere. I turned my chair to the fire and dozed. Again the atoms were gamboling before my eyes. This time the smaller groups kept modestly in the background. My mental eye, rendered more acute by the repeated visions of the kind, could now distinguish larger structures of manifold conformation; long rows sometimes more closely fitted together all twining and twisting in snake-like motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightning I awoke; and this time also I spent the rest of the night in working out the consequences of the hypothesis."* (Roberts, 1989)

**Sleep paralysis**

Sleep paralysis is a temporal muscle atonia, a transient heaviness or inability to perform voluntary movements, at the transition between wakefulness and sleep (Thorpy, 1990; Medicine, 2001). The person usually regains muscular control within a short time, one to several minutes. The paralysis is frequently accompanied by hypnagogic hallucinations in three main categories (Cheyne and Girard, 2007):

- Intruder experiences are sensory hallucinations which can be visual, auditory or tactile, often with fear. The feeling of a presence is also possible to occur.
- Incubus experiences on the other hand involve breathing difficulties, feelings of suffocation, smothering or choking, sensations of pressure or being crushed (for example, a weight pressure on the chest), and sometimes also pain and thoughts of death.
- Vestibulo-motor hallucinations are less associated with feelings of fear. They include sensations of floating, flying and falling, as well as feelings of bliss or euphoria.

Out of body experiences, *autoscopy* and illusory motor movements are also common.

*Autoscopy* is the experience of seeing oneself from an external point of view.

People may find these kinds of experiences rather puzzling and may be looking for an explanation; particularly if they have not come across them before (Sherwood, 2002). Anomalous interpretations are found in different cultures, e.g. *Old Hag* attacks in the Western world (Firestone, 1985) (Figure 2) or kanashibari in Japan (Fukuda et al, 1987), ghostly encounters and alien abductions (Blackmore and Cox, 2000).

The *Old Hag* is a folk belief of a nightmarish demon who sits on the chest of its victim, waking him up with a feeling of terror, inability to move and difficulty breathing because of the heavy weight on the chest (Figure 2).

### 1.2.3.4. Research methodology

Ancient authors had already mentioned the phenomenon in their writings after self obervation (Iamblichus, 1895 (orig. 3rd century AD); Aristotle, 1931 (orig. 4th century BC)-b, a). Romanticism brought a renewed interest in sleep and dreaming and authors described their own experiences (Poe, 1846; Saint-Denys, 1867), sometimes trying to find religious explanations (Swedenborg, 1746). Scientific research only began in the 19th century with the first *oneirologic* researchers who used introspective methods to meticulously describe hypnagogic imagery (Müller, 1826; Baillarger, 1846; Maury, 1848; Müller, 1848; Maury, 1853, 1857, 1865; Collard, 1953) and this continued in the early 20th century (Myers, 1892; De Manacéine, 1897; Ellis, 1897; Leroy and Tobolowska, 1901; Leaning, 1925; Leroy, 1926; Linschoten, 1952). Later on, more systematic procedures were developed, including upright napping (Nielsen, 1992), falling asleep while holding a spoon (Dalí, 1942) (Figure 3) or holding up one of the arms (Blackmore, 2003). Only since the late twentieth century, questionnaire surveys and experimental studies were used as well (Mavromatis, 1987). The invention of electroencephalography (Berger, 1929) meant a new revival in the research of hypnagogic hallucinations, complementing the introspective behavioral data with physiological recordings (Davis et al, 1937; Loomis et al, 1937b; Davis et al, 1938) and founding the research domain searching for neural correlates of hypnagogic imagery.

*Oneirology,* from Greek oneiros (dream) and logia (the study of), is the scientific study of dreams, examining correlations between dreaming and brain functioning, as well as the function of dreaming in memory consolidation and mental disorders. *Oneiric symbolism* means that certain objects are perceived in the dream or hypnagogic hallucination as something else (Sartre, 1940), e.g. the perception of spatial arrangement of colored shoe boxes as arrangement of Tetris blocks (Kussé et al, 2012).

Figure 2. Painting "The nightmare" by Henry Fuseli (1781) is a classic depiction of sleep paralysis perceived as a demonic visitation: it portrays simultaneously a dreaming woman and the content of her nightmare. The incubus and the horse's head refer to contemporary belief and folklore about nightmares.

A difficulty in studying hypnagogia lies in amnesia and the fleeting nature of hypnagogic experiences. These problems have been tackled by experimenters in a number of ways, including voluntary or induced interruptions (Germain and Nielsen, 1997), training introspection to heighten observation and attention (Blackmore, 2003) and techniques inducing or prolonging the duration of the hypnagogic state (Silberer, 1909; West, 1962; Green et al, 1970; Budzynski, 1972; Stoyva, 1973; Braud et al, 1975). However, it should be noted that these techniques may yield different brain functional states than in the natural transition to sleep (Schacter, 1976), although the subjective phenomena may seem very similar.

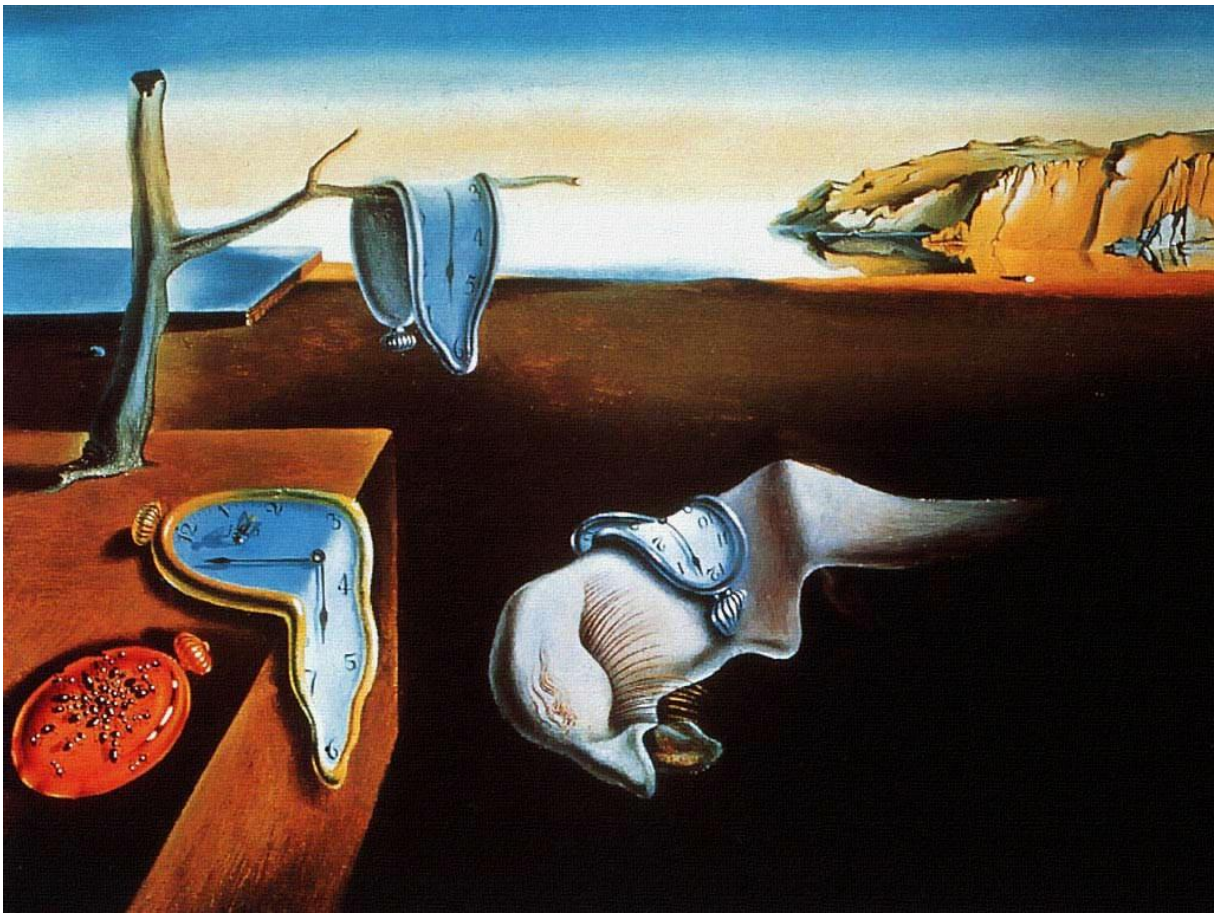

Figure 3. Painting "The persistence of memory" by Salvador Dalí, who was intrigued with the images which occur at the boundary between sleeping and waking. He experimented with various ways of generating and capturing these fantastical images. His favorite method was that he would put a tin plate on the floor and fall asleep while sitting on a chair with a spoon in his hand. As soon as he dozed off, he would drop the spoon. The loud clang on the plate would immediately wake him up to sketch the surreal images on a canvas. He called this a paranoiacritical method, in which he accessed his subconscious for greater artistic creativity.

## 1.3. Memory consolidation

To clarify our study about memory replay during resting state wakefulness, I will describe the basics of memory systems and memory maintenance in this chapter because the novelty of this experiment is to characterize memory consolidation directly, without confounding influences of retrieval.

The mental ability to store, retain, and recall information memories as long as years later is one of the most important aspects of human behavior. Humans are able to acquire new knowledge and we use our memories and in a way

that affects our lives every day. In fact, being able to memorize and access information is vital for survival. However, little is known about how new memories are formed, stored and accessed. The theory of memory consolidation states that patterns of brain activity generated during learning are spontaneously replayed afterwards, which has been examined with invasive techniques in animals and neuroimaging and computational methods in humans.

### 1.3.1. Memory systems

A major distinction can be made between sensory memory, short-term and long-term memory. In humans, we can further differentiate working memory, which is the capacity of holding information for very short periods of time (in the order of a few seconds or less) in the mind in order to complete complex tasks involving attention and executive aspects (Baddeley and Hitch, 1974; Baddeley, 2000).

Sensory memory includes separate stores for each modality: sight, hearing, smell, touch, and taste. These stores are assumed to serve as temporary buffers from which information can be accessed for a very short time, namely the initial 200 - 500 milliseconds after an item is perceived through one of the senses (Jiang, 2004), after which they are lost due to decay or to interference from more recent stimuli (Winkler and Cowan, 2005). The short time window of sensory memory is just long enough for the information to be transferred to short-term memory. The capacity of sensory memory is approximately 12 items, degrading very quickly. This type of memory cannot be prolonged via rehearsal.

In short-term memory, memories are stored for a very small duration, ranging from seconds to a minute, without rehearsal, and with a very limited capacity, usually 4 or 5 items (Miller, 1956) although this can be enhanced by *chunking*.

*Chunking* is a process whereby responses are grouped to more effectively perform a memory task. An example is recalling a telephone number in groups, e.g. the area code 04, and the chunks 366 and 23 and 03.

On the other hand, in the long-term, memories are available for retrieval after months or years, up to a whole life span, with a huge storage capacity. Long-term memory can be

differentiated further into different memory systems (Anderson, 1976) (Figure 4):

- The declarative or explicit memory system stores information that can be consciously recalled, such as autobiographical memories, textbook knowledge, facts, events, places and dates. For instance, semantic memories pertain to common knowledge (e.g. what is the capital of Belgium) and episodic memories pertain to specific individual life events for which both content and context can be consciously recalled and verbalized (e.g. the first date with your husband or wife) (Schacter and Tulving, 1994). The hippocampus in the medial temporal lobe is essential for integrating new episodic information, as has been found in *patient HM*.

Henry Gustav Molaison, known as *patient HM*, was a widely investigated memory disorder patient after his hippocampi, parahippocampal gyri and amygdalae were removed in an experimental brain surgery attempting to cure epilepsy. His case gave important insights into memory function and the underlying neural structures (Scoville and Milner, 1957).

- The non-declarative or implicit memory system, also called procedural memory, contains information which cannot be consciously recalled and verbalized, such as skills, habits, procedures, abilities (e.g. how to ride a bike or playing piano).

### 1.3.2. Encoding, consolidation and retrieval

In the study about memory replay, we aim at visualizing memory consolidation in a direct manner without confounding influences of retrieval of that information or concurrent encoding of new material. Therefore, in this section I will first clarify the three main stages of memory processing. Then, consolidation, which is our main point of interest, will be described more in detail.

<table>
<tr><th colspan="2">Declarative, explicit</th><th colspan="2">Non-declarative, implicit</th></tr>
<tr><td rowspan="2">Behavioral: verbal paired associate learning tasks (i.e. word-pairs and cued-recall; nonsense syllables; objects location; short stories; and word lists</td><td>- conscious<br>- based on facts<br>- flexible<br>- readily acquired during relatively few exposures to events or facts</td><td>- non-conscious<br>- less flexible<br>- requires much longer exposure and repetition of actions</td><td rowspan="2">Motor memory: FTT; SRTT; perceptual skills; visual texture discrimination; sensory skills; mirror tracing; others: visuo-motor discrimination</td></tr>
<tr><td>Episodic<br>- events of individual's past (e.g. spatio-temporal recollection)<br><br>Semantic<br>- general knowledge not related to events (but related to facts)</td><td>Procedural<br>- learning of skills<br>- habits<br>- actions<br><br>Implicit<br>- exposure<br>- perceptual learning<br>- priming</td></tr>
</table>

Figure 4. Memory systems with examples of tasks, often used in research, recruiting one specific memory system. FTT: finger tapping task; SRTT: serial reaction time task. Figure adapted from (Shaffii-Le Bourdiec et al, 2010).

Three main processes are always underlying the establishment of permanent memories, regardless of their type (Squire et al, 1984):

- Encoding or registration includes the acquisition, processing and combining of incoming information at first encounter, which depends on motivation and attention. The new information enters the brain along pathways between neurons in the appropriate brain area.

- *Consolidation* or storage, refers to the processes during which the labile encoded information is altered by the hippocampus to create a more permanent cortical record which can be stored over a longer time period.

- Retrieval or recall refers to the processes that permit calling back the information on purpose in response to some cue, for use in a process or activity. We can

*Memory consolidation* has been proposed already a century ago (Müller and Pilzecker, 1900). Moreover, ancient rhetoricians already noted that *"The interval will greatly increase the strength of the memory… the power of recollection, which is the most important element of memory, undergoes a process of ripening and maturing during the time which intervenes, as to strengthen the memory"* (Quintilian, 1st century AD).

distinguish passive recognition (whether the subject has encountered a stimulus before) and active recall memory (requiring the subject to reproduce previously learned information). The more frequently the information is accessed, the easier it is to retrieve it.

The *synaptic downscaling* hypothesis assumes a progressive synaptic potentiation throughout the brain during wakefulness (Tononi and Cirelli, 2006). Slow oscillations during subsequent NREM sleep are generated in proportion to local neuronal work (Kattler et al, 1994) and learning during previous wakefulness (Huber et al, 2004), and their decline during sleep would reflect the recalibration of synaptic efficacy (Vyazovskiy et al, 2009).

Although most researchers agree on the exposed framework for treatment of memory traces, many details of this process are still unknown, especially regarding mnemonic consolidation (Miller, 2012). Nowadays, we know that the time course of memory consolidation consists of several dynamic processes after initial encoding of new information (for a review, see (Frankland and Bontempi, 2005)): synaptic consolidation, which occurs within the first few minutes to hours following acquisition; system consolidation, which occurs over weeks to years, or alternatively the *synaptic downscaling theory*; and recently a third process of reconsolidation has been suggested. These processes will now be described in more detail.

*Long-term potentiation (LTP)* is a prolonged strengthening of synaptic transmission between neurons, resulting from synchronous stimulation. LTP can be thought of as a neural correlate of memory (Cooke and Bliss, 2006).

First, synaptic or cellular, local consolidation occurs, necessary for the initial stabilization of memories. This process is marked by altered protein synthesis, the growth of new synaptic connections as well as the restructuring of existing synapses. They depend on a cascade that is initiated by synaptic activation, which leads to the recruitment of second messenger systems, activation of transcription factors and, ultimately, synthesis of new proteins required for the structural changes (*long-term potentiation* (Frankland et al, 2001; Hayashi et al, 2004)). Any manipulation that interferes with any part of this cascade will block memory formation. This synaptic reorganization takes place in the minutes and hours following encoding (Squire and Kandel, 2000; Dudai, 2004).

Second, occurring on a larger timescale (over a period of weeks to years), system consolidation takes place during which the memories are reorganized. Initially, declarative memories are stored in cortical areas whereas the hippocampus integrates this information (Eichenbaum, 2004). During system consolidation, spontaneous reactivation of these hippocampo-cortical circuits will progressively transfer all information to the cortical areas

which, by firing together, will progressively connect (Figure 5) (*Hebb's rule*). The memories would eventually be stored mainly (Nadel et al, 2000) or exclusively (Frankland and Bontempi, 2006) in neocortical areas, depending on the memory system (Figure 6), and would thus become relatively independent of the hippocampus. It has been suggested that the medial prefrontal cortex would take over the integrating function of the hippocampus (Takashima et al, 2006). Spontaneous reactivations of these memory traces can occur both during wakefulness (Hoffman and McNaughton, 2002) and sleep (Ribeiro et al, 2004), which will be further elaborated in the next chapter.

Third, reconsolidation may happen, in which previously consolidated memories can be turned back into a labile state through recalling the memory trace (Walker et al, 2003). Reconsolidation can be considered as a never ending process of consolidation and reorganization of memory traces: new memories hence become integrated and interleaved within a large network of relevant pre-existing knowledge (McKenzie and Eichenbaum, 2011).

Importantly, during consolidation, memories are labile and easily perturbed. Therefore, the events between encoding and recall will influence the quality of the recollection. Such interfering processes can range from pharmacological administrations (e.g. protein synthesis blockers or receptor antagonists (Gais et al, 2008)), physiological stimulations such as transcranial magnetic stimulation (Ruzzoli et al, 2010), or simply behavioral interference with newly encoded information (Ellenbogen et al, 2006).

*Hebb's rule* explains the adaptation of neurons in the brain during the learning process: *"Let us assume that the persistence or repetition of a reverberatory activity (or trace) tends to induce lasting cellular changes that add to its stability.... When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased"* (Hebb, 1949). It is often summarized as *"Cells that fire together, wire together."*

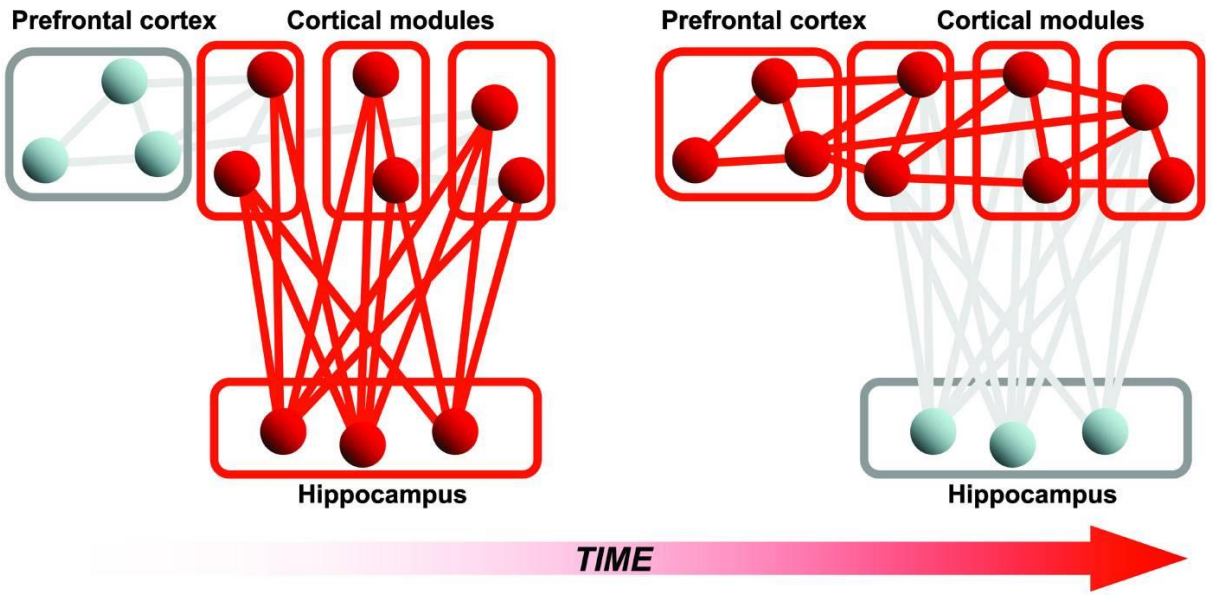


Figure 5. Time-dependent memory reorganization. Memory recall depends on integration of information from a large number of cortical sources. This function is initially carried out by the hippocampus, but with time, it is taken over by the medial prefrontal cortex, allowing memories to become independent of the hippocampus and to be gradually integrated with pre-existing cortical memories (McClelland et al, 1995; Squire and Alvarez, 1995). Reactivation of this network leads to progressive strengthening of cortico-cortical connections (for example, by strengthening the existing connections or establishing new ones). Figure from (Frankland and Bontempi, 2006).

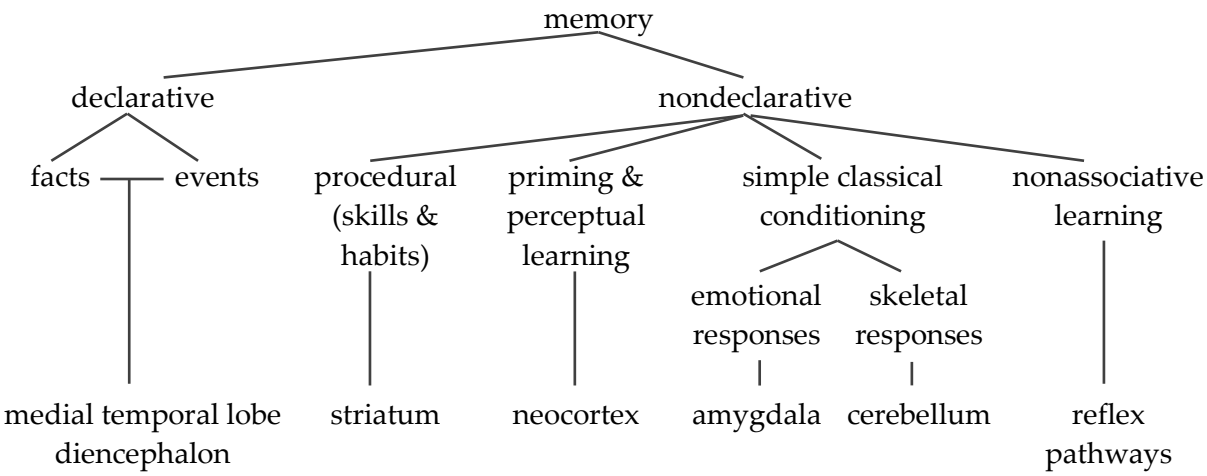


Figure 6. Different memory systems and the corresponding brain areas. Figure adapted from (Gazzaniga, 2009).

### 1.3.3. Replay

Although the mechanisms by which a recent labile episodic memory trace is consolidated to a long-lasting trace are not yet fully understood (McGaugh, 2000), it has been suggested that *offline* processing and spontaneous repetitions of brain activity patterns could play a role in consolidating recently formed memory traces. The neural correlates of memory consolidation remain to be characterized directly, and this is the aim of our second study.

An important factor in the consolidating process is that it takes place when no further information has to be processed, i.e. predominantly *when the cortex is offline* during sleep and resting state wakefulness, in order to prevent interferences. Concurrent competing retrieval of older memories impairs retrieval of newer memories (Kuhl et al, 2012a).

Multi-unit recordings in animals show that neural activity during post-task wakefulness or sleep indeed tends to repeat cell firing patterns recorded during training. Such reactivation of mnemonic traces has been detected in rats during slow wave sleep (Pavlides and Winson, 1989; Ji and Wilson, 2007), rapid eye movement sleep (Louie and Wilson, 2001) and wakeful resting state (Foster and Wilson, 2006) and in primates during rest (Hoffman and McNaughton, 2002). Using voltage-sensitive dye-imaging, activity motifs are replayed spontaneously during light anesthesia and wakefulness in mice (Mohajerani et al, 2013). These neural activities are deemed spontaneous, as they are elicited in the absence of relevant external stimuli or cues.

The information given by these animal studies would be nearly impossible to obtain in healthy humans, given the invasive nature of the protocols such as single or multi-cell intracranial recordings, histological marking, etc., although task learning is not as rapidly achieved in rodents and other primates as in humans. Because our study population consists of healthy human participants, we will now have a look at the properties of memory replay in humans in more detail.

In humans, it is known that spatial activity patterns are correlated with functional organization of preceding wakefulness (Ramot et al, 2013) and that declarative memories can be reactivated by cues (Rasch et al, 2007; Diekelmann et al, 2011; Staresina et al, 2013) and by associations (van Dongen et al, 2012).

During post-task wakefulness, task-learning modulates regional brain responsiveness to other incoming stimuli (Peigneux et al, 2006) and influences spontaneous brain activity (Tambini et al, 2010; Deuker et al, 2013; Tambini and Davachi, 2013). Moreover, replay of brain activity has been detected immediately after encoding (Jafarpour et al, 2014). In other experiments, imagery of complex everyday experiences could be reliably decoded from brain activity in the human hippocampus (Chadwick et al, 2010; Deuker et al, 2013). Although these studies only brought indirect insight in the mechanism of memory consolidation, they confirm the animal studies.

Temporally sequenced information seems to be conserved during replay suggesting that the structure of the learning material (the phase information) has to be maintained during consolidation of memories. Likewise, during post-learning periods, rodent multi-unit recordings showed that neurons tend to fire following similar temporal sequences as during learning, thereby preserving the temporal configuration associated with the learned material across cells either in a forward (Siapas and Wilson, 1998; Kudrimoti et al, 1999; Nadasdy et al, 1999; Louie and Wilson, 2001; Lee and Wilson, 2002; Diba and Buzsaki, 2007; Euston et al, 2007) or backward sequence (Foster and Wilson, 2006; Diba and Buzsaki, 2007) (Figure 7).

It seems that the temporal order of activation should be preserved at the macroscopic level, namely across brain areas, if the material to be learned imposed such a strict temporal structure. In support of this, associative learning memory of a temporal sequence is characterized by both forward and backward associations among the stored items of the sequence, with forward associations showing stronger bonds (Kahana, 1996; Howard et al, 2005; Drosopoulos et al, 2007).

Furthermore, the strength of the reactivations seems to be linked to behavioral performance (Peigneux et al, 2004; Peigneux et al, 2006; Girardeau et al, 2009; Tambini et al, 2010). Indeed, a disruption of memory consolidation during post-training sleep by hippocampal stimulation resulted in impaired behavioral task performance (Girardeau et al,

2009). Moreover, the amount of hippocampal activity during deep NREM sleep is related to the overnight improvement in behavioral performance (Peigneux et al, 2004). In other studies, brain responses to an unrelated task are modulated by a previous learning task and this post-training activity correlates with behavioral performance (Peigneux et al, 2006; Kuhl et al, 2011). An enhanced correlation between the hippocampus and the neocortex during post-task rest compared to baseline rest has been shown as well, which predicted individual differences in later associative memory (Tambini et al, 2010).

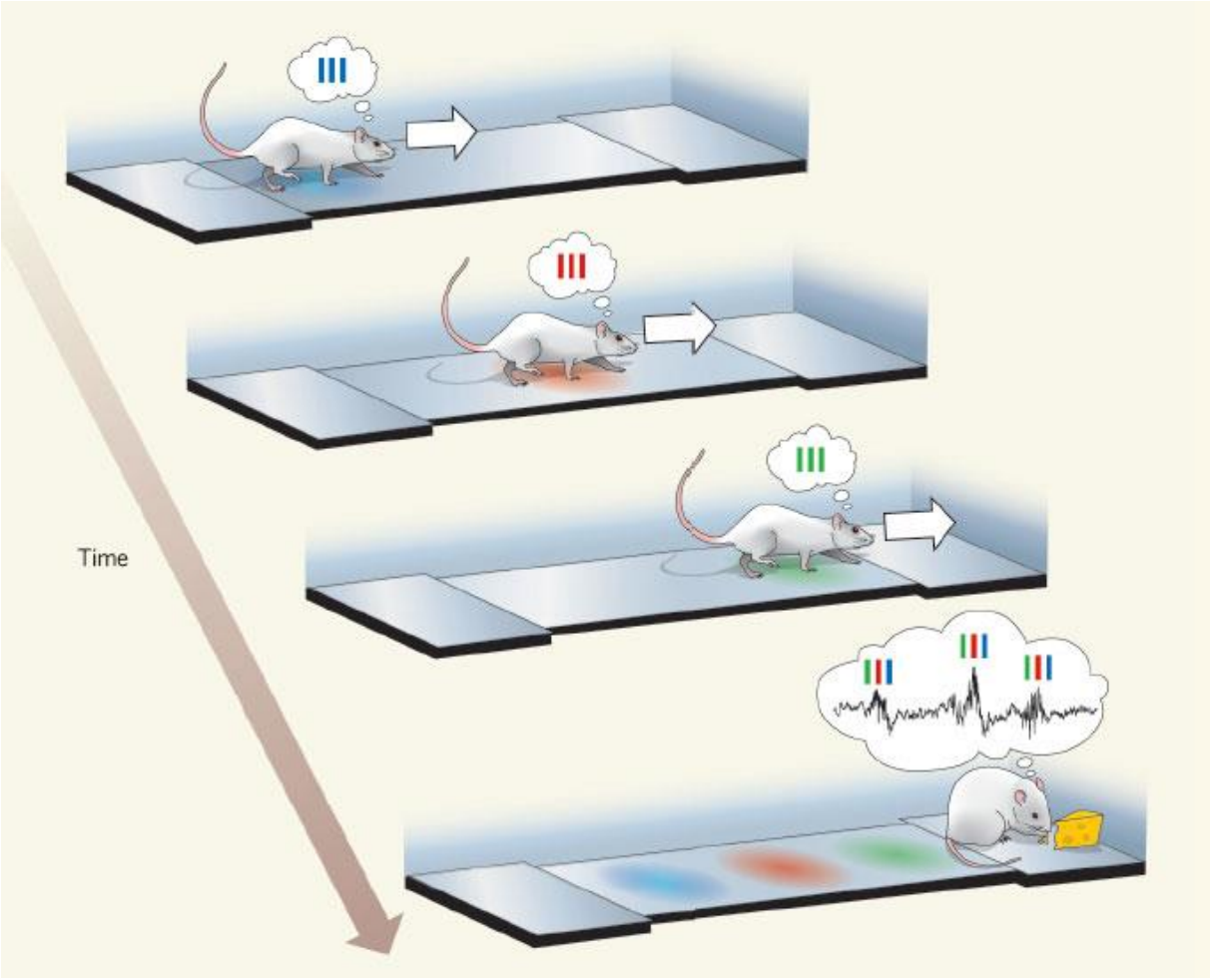


Figure 7. Reverse replay. Three place cells (blue, red and green) in the hippocampus fire as a rat runs on a linear track. The colored lines represent firing of place neurons. When the rat is rewarded with food at the end of the linear track, the hippocampal firing sequences ar replayed in reverse (i.e. green, red, blue). Figure from (Colgin and Moser, 2006) explaining the experiment from (Foster and Wilson, 2006).

Finally, animal studies showed that reactivations of previously active cell assemblies occur preferentially during the first half hour after exploration (Kudrimoti et al, 1999; Girardeau et al, 2009) with a decay constant of 12 (Wilson and McNaughton, 1994) à 13 (Kudrimoti et al, 1999) to 30 minutes after the encoding (Ji and Wilson, 2007). On the other hand, human studies found no effect of time on seed correlations in a 10 minute rest period (Tambini et al, 2010). The time frame of the repeated patterns also seems to be scaled, as several experiments have yielded a variable compression factor in SWS from 5-10 times compression (Ji and Wilson, 2007), 6 to 7 fold (Euston et al, 2007) to a 20 fold compression in SWS (Lee and Wilson, 2002). In REM sleep, replayed activity patterns were reported on a similar timescale (Louie and Wilson, 2001).

### 1.3.4. Limitations and challenges

Although the animal studies in the previous paragraphs support the theory of memory consolidation and give hints on its temporal aspect, they do not allow a non-invasive and direct characterization of mnemonic traces during resting state wakefulness in humans.

**Behavioral challenge: characterizing consolidation**

In humans, memories are usually probed either during encoding (Kuhl et al, 2012b; Jafarpour et al, 2014) or during retrieval (Polyn et al, 2005; Chadwick et al, 2010; Kuhl et al, 2011; Staresina et al, 2013) with non-invasive neuroimaging techniques but their latent status between these two steps, consolidation, is more difficult to examine because this is a spontaneous phenomenon of which the temporal and spatial distributions are not yet understood. Usually, this problem is avoided by asking the subject to recollect the learned information. However, in this case the characterization of the memory trace is contaminated by processes engaged in retrieval of the learned item (Gais et al, 2007; Sterpenich et al, 2007; Albouy et al, 2008). In order to avoid such confounding effect, experimental protocols have been developed during which the cerebral responses to a probe task are modified by previous learning experiences (Peigneux et al, 2006; Kuhl et al, 2011).

Nevertheless, although no retrieval effort is asked from the volunteers, the characterization of the memory trace stays indirect.

**Methodological challenges**

Examining spontaneous activity in resting state, eyes closed and not submitted to any external stimulation, is a better option but this methodology represents other challenges, namely the huge dimensionality of the data and the absence of a ground truth. Up to now, typical research designs aimed at reducing the dimensionality of the data (Margulies et al, 2010), for example by computing activation maps in a standard GLM analysis or by selecting regions of interest. Although mass univariate analysis (Friston et al, 2007) brought indirect insight on regionally specific inferences on brain function and structure (Peigneux et al, 2006; Tambini et al, 2010), confirming what was shown in animals using intracranial recordings, there are *limitations* on examining voxels in a mass univariate fashion.

In order to characterize memory consolidation directly on a macroscopic level, brain decoding or mind reading techniques are the most appropriate techniques. These techniques consist in predicting the individual mental representations, conscious or not, based on an objective measurement of brain activity (Haynes and Rees, 2006) (Figure 8).

*Limitations of mass univariate analysis:*
- Spatially distributed sets of voxels considered outside the peak areas that are labeled as non-significant by the SPM analysis of an experimental condition, might still carry information, and hence contribute to a more accurate classification. Including only the peak category-selective regions of interest has been shown to yield a less sensitive classification (Polyn et al, 2005).
- The independent and identically distributed (IID) assumption of SPM is often not met because neighboring voxels are not independent of each other.
- Classic mass univariate analyses are mainly designed to perform group-wise comparisons and would therefore be unsuitable to evaluate the mental state of an individual.

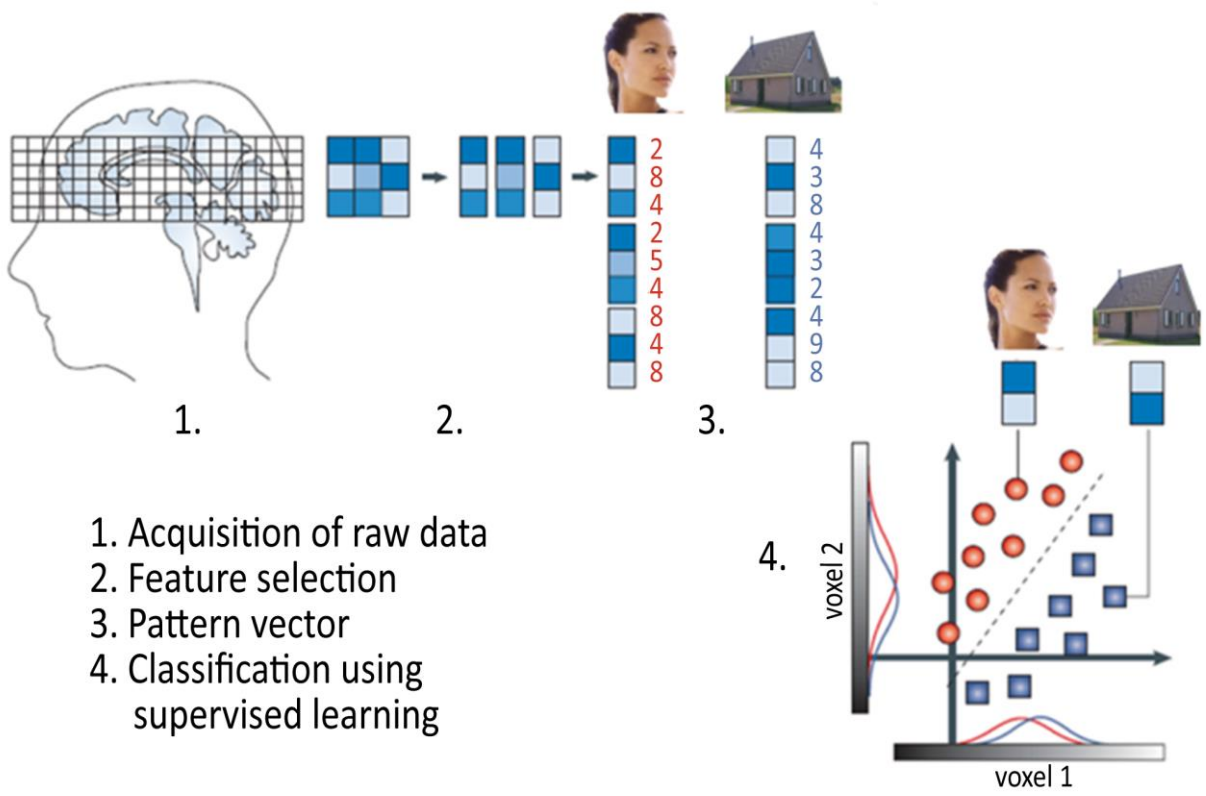


Figure 8. Multivariate pattern recognition approach. 1. fMRI measures brain activity repeatedly every few seconds in a large number of voxels (usually covering the whole brain). 2. Feature selection: joint activity in a subset of these voxels (here a 3x3 grid) constitutes a spatial pattern. 3. This spatial pattern can be expressed as a pattern vector (here a 9x1 vector). Different pattern vectors reflect different mental states; for example, those associated with different viewed pictures. 4. Classification using supervised learning. Each pattern vector can be interpreted as a point in an N-dimensional space (shown here only the first two dimensions, red and blue indicate the two conditions). Hence, each scan of the fMRI time series corresponds to a single point. A successful classifier learns to distinguish between pattern vectors measured under different conditions. The parameters of the decision boundary (expressed as a mathematical function, i.e. a classifier) are computed by the algorithm. Figure and caption adapted from (Cox and Savoy, 2003; Haynes and Rees, 2006).

## 1.4. Functional brain specialization

Our experiment of memory replay is based on the characteristic specialization of visual areas, namely regions that show activity when recognizing faces, buildings and animals. Therefore, we summarize the main aspects of visual object recognition and category-specific visual brain areas.

The visual system consists of at least two parallel processing streams (Figure 9), which are each specialized for a specific functional task. The dorsal stream, also referred to as the

*where* (Mishkin and Ungerleider, 1982), *how* or *action* stream (Goodale and Milner, 1992), has been associated with spatial localization, movement and manipulation or visually guided action; and the ventral *what* stream (Mishkin and Ungerleider, 1982), is accounting for scene and object recognition, perception and categorization.

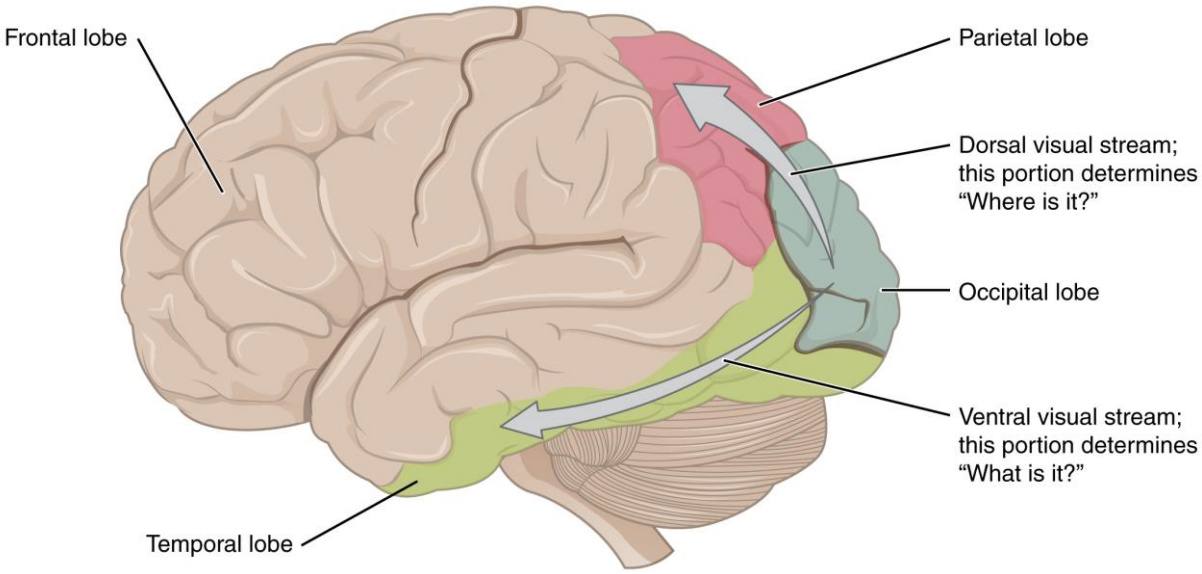


Figure 9. From the primary visual cortex, visual information is transferred to secondary association cortices in the dorsal where and ventral what stream. (Figure from cnx.org)

The brain contains several areas that exhibit selective responses to a variety of visual stimuli (for overviews, see (Zeki, 1990; Hasson et al, 2003; Grill-Spector and Malach, 2004; Downing et al, 2006)). Such category-selective regions respond more strongly when subjects view pictures of objects than nonobject controls such as textures, visual noise or scrambled objects (Grill-Spector et al, 1998) or other objects (Downing et al, 2006). The human object-selective regions (Figure 10) respond to buildings, faces, tools, chairs, animals, common objects, kinetic movement, body parts, motion objects, illusory contours, words, and somatosensory objects.

In this work, we will focus on the FFA (fusiform face area) which is selective for faces, the PPA (parahippocampal place area) which responds to scenes and buildings, and the region responding specifically to animals which we call AA (animal area) for the sake of simplicity (Downing et al, 2001). Given their functional proprieties, they are ideal to

study the influence of resting state wakefulness on offline memory processing:

- Perceptual invariance (Grill-Spector et al, 2004): as long as the object is perceived, the way of presenting the object does not matter to obtain equal brain activity in the ventral visual stream, which is handy to examine imagery and spontaneous processing of visual stimuli.
- Unfamiliar, novel stimuli, activate the category-specific regions more than familiar stimuli (Dolan and Fletcher, 1997; Epstein et al, 1999). On the other hand, common familiar objects that are easily named elicit the least activation (Gauthier et al, 2000). In support of this, awake replay of novel stimuli seems to be more prevalent than of familiar ones (Foster and Wilson, 2006; Diba and Buzsaki, 2007).

*Two theories exist about the function of the FFA:*
- One group of researchers suggests a *flexible process map* in which the FFA would be activated by objects of expertise and a high level of categorization, such as faces in most people but also cars seen by car experts, birds by bird experts, and so on (Gauthier et al, 2000; Tarr and Gauthier, 2000).
- The most widely accepted theory however is the *detection model*: face selectivity in the FFA would reflect an innate mechanism for detecting the geometry of faces (Kanwisher, 2000).

**FFA: fusiform face area**

By comparing the response to faces and non-face objects, it is possible to evaluate the *function of the FFA*. Evidence comes from PET (Kanwisher et al, 1997b), fMRI (Kanwisher et al, 1997a; Gauthier et al, 2000), EEG (Allison et al, 1999; McCarthy et al, 1999; Puce et al, 1999), *prosopagnosia* (Bentin et al, 1999) and dynamic causal modeling (Mechelli et al, 2003).

*Prosopagnosia*, from the Greek prosopon (face) and agnosia (not knowing) is also called face blindness, which is a disorder where the ability to recognize faces is impaired.

**PPA: parahippocampal place area**

The response in the PPA to scenes with spatial layout but no discrete objects (e.g. empty rooms) is as strong as the response to complex meaningful scenes containing multiple objects (e.g. the same rooms furnished) and much stronger than the response to objects without spatial context (e.g. the furniture from these rooms on a blank background) (Epstein and Kanwisher, 1998).

**Brain specialization for animate stimuli**

Recognition of animals is associated with activation of an area in the ventral (fusiform gyrus) posterior temporal lobes (Martin et al, 1996; Chao et al, 1999), which we call AA (animal area) in this thesis.

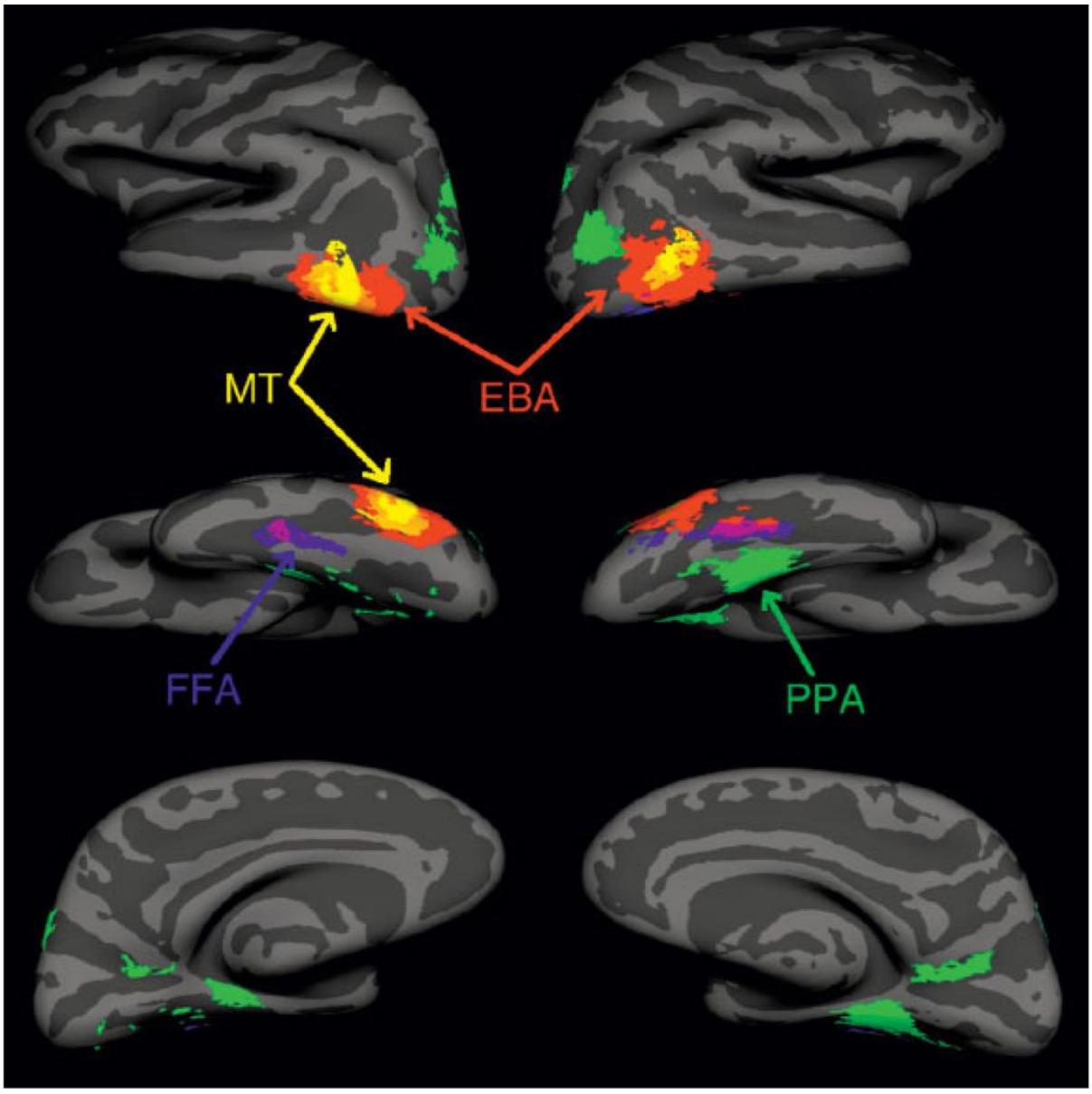


Figure 10. Regions shown on lateral (top), ventral (middle), and medial (bottom) views of the cortical surface of an averaged template brain, left hemispheres on the left part and right hemispheres on the right part. Figure from (Spiridon et al, 2006).

# 2. OBJECTIVES

In this work, we aim to investigate human spontaneous brain activity and its relationship to early memory processing, using multimodal techniques. To this end, we have conducted two main studies:

- A behavioral study of hypnagogic hallucinations at sleep onset during daytime naps after task practice, while volunteers were online monitored with polysomnography consisting of electrooculography, electromyography and a basic electroencephalogram. Behavioral questionnaires and verbal reports of the hypnagogic hallucinations were recorded and further investigated.
- A study of resting state wakefulness after task learning, while participants were scanned continuously with functional magnetic resonance imaging. Time series were meticulously explored with four state-of-the-art techniques (dynamic causal modeling, correlations and explained variance, identification of spatial networks based on independent component analysis, and multivoxel pattern analysis based on machine learning techniques).

Our first goal is to examine whether explicit learning would lead to an increase in task-related brain activity. It needs to be confirmed whether learning of a visuospatial task can induce task-related spontaneous reactivations immediately afterwards and whether these reactivations contain the same modalities as the task itself. It will be interesting to see whether these spontaneous reactivations can reach the level of consciousness, namely as hypnagogic hallucinations at sleep onset or thoughts during resting wakefulness.

The second important objective is to relate reactivation to memory performance. If spontaneous reactivations of task-related brain activity play a role in offline memory processing, it would be logical that they improve subsequent performance, and this only in the memory condition, not in the control condition.

The third aim is to see if the temporal structure of the encoding events is preserved during reactivation, if the learned task imposes a strict temporal sequence of brain activity patterns.

# 3. RESEARCH STUDY 1: SLEEP ONSET

This chapter is based on:

*Kussé C*, Shaffii-Le Bourdiec A, Schrouff J, Matarazzo L, Maquet P (2012) Experience-dependent induction of hypnagogic images during daytime naps: a combined behavioural and EEG study. J Sleep Res 21(1): 10-20.

Significance

This study characterizes hypnagogic hallucinations reported during a polygraphically recorded daytime nap following or preceding a task (the computer game Tetris). We found that task-related hypnagogic hallucinations were more consistently induced by experience than by anticipation, incorporating the same modalities of the task, and they were predominantly observed during the transition of wakefulness to sleep.

## 3.1. Objectives

The aim of this study is to characterize at a behavioral level the spontaneous processing of visuospatial learning, via the appearance of task related hypnagogic hallucinations.

The present study is conducted in the framework of a broader research effort which attempts to characterize the cerebral correlates of conscious processes like thoughts, hypnagogic hallucinations and dreams during the different states of consciousness. However, studying the stream of consciousness using objective methods like EEG or fMRI is difficult for two reasons: it is unconstrained and unpredictable. In this context, studying hypnagogic hallucinations is an interesting model because their content and timing can be experimentally constrained.

Hypnagogic hallucinations are conscious mental representations that emerge spontaneously at sleep onset. Early observations dating back to the XIXth century suggested that stereotypical hypnagogic imagery can be related to the sensory stimuli during previous waking activities (Maury, 1865; Ward, 1883; Myers, 1892; Leroy, 1926; Vihvelin, 1948; Hanawalt, 1954; McKellar, 1957; Hebb, 1968). Recent studies experimentally confirmed that incorporation of stereotypical images into nighttime sleep-onset mentation can be induced by prior practice of video games, such as Tetris (Rowley et al, 1998; Stickgold et al, 2000), or Alpine Racer, a downhill skiing game (Emberger, 2001; Stickgold et al, 2001a; Wamsley et al, 2010). However, several features of this intriguing phenomenon are still incompletely characterized.

First, experience-related hypnagogic hallucinations were exclusively reported during nighttime sleep onset (Stickgold et al, 2000; Wamsley et al, 2010). However, it was not known whether this phenomenon was restricted to nocturnal sleep and whether naps would be as efficient in eliciting it. Although it is known that other sleep-related spontaneous mental experiences, such as dreams, follow a circadian modulation (Chellappa et al, 2009), and daytime sleep is usually shorter and shallower and with longer sleep-onset latency (Carskadon and Dement, 1977;

Carskadon et al, 1986), the occurrence of hypnagogic hallucinations during daytime sleep, beyond individual experience and some anecdotal evidence (Stickgold et al, 2000), has not yet been experimentally assessed.

Second, the vigilance state in which experience-related hypnagogic hallucinations can be induced is still to be firmly characterized. As a rule, hypnagogic hallucinations occur in a specific state of vigilance at the transition of wakefulness to sleep, which corresponds to sleep stage 1 (Foulkes and Vogel, 1965; Hori et al, 1994; Rowley et al, 1998). At odds with these findings, it was recently suggested that experience-related hypnagogic hallucinations might also occur during waking and sleep stage 2 (Stickgold et al, 2000; Wamsley et al, 2010). However, these conclusions were not derived from standard polygraphic recordings and the vigilance state associated with experience-dependent hypnagogic hallucinations remains to be firmly established.

Third, the nature of these experience-related hallucinations has not yet been thoroughly investigated. After Tetris practice, they were categorized in images and thoughts about the game (Stickgold et al, 2000). After Alpine Racer training, they consisted of thoughts or visual and kinesthetic perceptions, directly or indirectly related to the task (Wamsley et al, 2010). A more detailed characterization of the hallucinatory material is important because it might shed some light on the underlying organization of brain function (Schwartz and Maquet, 2002).

Fourth and finally, the origin of hypnagogic hallucinations has to be experimentally confirmed in different groups of volunteers: does anticipation on task practice, as reported by (Wamsley et al, 2010) have a similar effect as genuine task experience on the mental content at sleep onset? Moreover, it remains uncertain whether experience-related hypnagogic hallucinations reflect active memory processes or simply indicate the increased readiness to fire of neural populations whose synaptic connections were recently strengthened. In support of the former assumption, the probability of induction of hallucinations after playing Tetris tended to be negatively correlated with initial

performance, suggesting that individuals who reported most hallucinations at sleep onset were those with the largest potential learning range (Stickgold et al, 2000).

Here we address these different issues and characterize hypnagogic hallucinations in a between-subjects design, in three groups of volunteers who practiced Tetris (experimental and anticipation groups) or not (control group) using iterative awakenings during polygraphically-monitored daytime naps.

## 3.2. Material & methods

### 3.2.1. Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. During recruitment, all participants of all groups were fully informed about the protocol and EEG. This information was repeated on arrival at the lab. All gave their written informed consent.

### 3.2.2. Population

The participants were mainly recruited through the forum of the website of the University of Liège (www.ulg.ac.be) and were paid for their participation. They were young (age 18-33), non-smoking, right-handed healthy volunteers. The absence of medical, traumatic, psychiatric or sleep disorders was established in a semi-structured interview using standardized questionnaires.

None complained of excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale ((Johns, 1991); scores ≤ 10), nor of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire ((Buysse et al, 1989); score ≤ 6). All participants had normal scores on the Beck Anxiety Inventory ((Beck et al, 1988); score ≤ 7) and the Beck Depression Inventory II ((Steer et al, 1997); scores ≤ 13). They were right-handed as indicated by the Edinburgh Inventory (Oldfield, 1971). Extreme chronotypes according to the Horne and Ostberg morningness-eveningness questionnaire were excluded ((Horne and Ostberg, 1976); scores < 30 and > 70). They were moderate

caffeine and alcohol consumers and none was on medication (except oral contraceptives for women). None had worked on night shifts or traveled across more than one time zone during the last two months. Participants did not have extensive prior experience in computer games (e.g. Tetris). The amount and content of their dreams was examined with the Waterloo unusual sleep experiences scale, London sleep and dream questionnaire, and dream diary.

Subjects were instructed to eat normally but to abstain from stimulants (such as coffee, tea, coca cola, red bull, etc.) and cigarettes. They were asked to maintain a regular sleep-wake rhythm without daytime naps in the seven days before and during the experiment. During this period, their sleep-wake cycle was assessed by a sleep agenda and wrist actigraphy (Actiwatch, Cambridge Technology, UK). Volunteers who showed deviations for more than 15 minutes from the habitual sleep-wake schedule, were excluded. All questionnaires were presented in the volunteer's native language, i.e. French, Dutch or English.

### 3.2.3. Experimental design

#### 3.2.3.1. General overview

Three groups were examined (Figure 11):

**1) Tetris group** (Figure 11 top): The experiment was run on three consecutive days. In the morning of each experimental day, six hours after sleep midpoint (SMP), the volunteers were asked to play Tetris.

**2) Control group** (Figure 11 middle): A separate control group of volunteers followed exactly the same protocol as the Tetris group, except that the experiment was run on a single day and that volunteers did not practice Tetris at all. They stayed in the laboratory and were allowed to read but not play card or computer games.

**3) Anticipation group** (Figure 11 bottom): A third separate group of volunteers was examined during one single day and again followed exactly the same protocol as the Tetris

group, except that the Tetris practice session was scheduled after the afternoon nap.

At noon, the volunteers received a light meal and were prepared for polygraphic recordings, which included EEG, EOG and EMG (for details, see 3.2.4.1). Ten hours after individual sleep midpoint, volunteers were asked to sleep in a quiet room at the laboratory under constant polygraphic monitoring. They could interact with the experimenter through an intercom, and were wearing a headset.

In all groups, subjective sleepiness and vigilance were measured four times throughout the experimental day: before and after task practice in the morning, and before and after the afternoon nap. The latter PVT was conducted after the removal and cleaning of the electrodes to avoid post-sleep drowsiness.

#### 3.2.3.2. Assessment of sleepiness and alertness

A psychomotor vigilance task (PVT) was used to estimate vigilance for 5 minutes by measuring the motor reaction time (pressing a response button with the thumb of the dominant hand) to a visual stimulus which was presented using random interstimulus intervals ranging from 1 to 9 seconds (Dinges and Powell, 1985; Kribbs and Dinges, 1994; Loh et al, 2004; Kaida et al, 2006). The PVT was conducted before and after the Tetris practice sessions, and before and after the 90 minute afternoon nap.

The Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990; Akerstedt et al, 1994) is a subjective ranking of alertness by the subject itself (on a 9 point scale; 1 being very alert, 3 normal level of alertness, 5 neither alert nor sleepy, 7 sleepy but not fighting sleep, 9 very sleepy and fighting sleep), and was asked before and after the Tetris practice sessions, after each completed Tetris game, before and after the 90 minute afternoon nap, and at every awakening during the nap.

| Group | SMP + 6.00h | | | Lunch | | SMP + 10.00h | | | | | SMP + 11.30h | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tetris | KSS PVT | Tetris 8x15′ | KSS PVT | Calibrated snack Electrodes PSG | KSS PVT | Recording during nap + awakenings at 15″ KSS | 45″ KSS | 75″ KSS | 120″ KSS | 180″ KSS | KSS PVT | / |
| Control | KSS PVT | / | KSS PVT | Calibrated snack Electrodes PSG | KSS PVT | Recording during nap + awakenings at 15″ KSS | 45″ KSS | 75″ KSS | 120″ KSS | 180″ KSS | KSS PVT | / |
| Anticipation | KSS PVT | / | KSS PVT | Calibrated snack Electrodes PSG | KSS PVT | Recording during nap + awakenings at 15″ KSS | 45″ KSS | 75″ KSS | 120″ KSS | 180″ KSS | KSS PVT | Tetris 8 x 15′ |

Figure 11. Time schedule of the study design for one experimental day. The same protocol was followed across three days in the experimental Tetris group.

#### 3.2.3.3. Tetris

The aim of this popular puzzle computer game is to complete horizontal lines of blocks without gaps, by manipulating colorful tetrominoes while they are falling down the playing field (Figure 12). The version of Tetris used in this study is adapted from a freely available Matlab code from which performance scores can be derived (Pascal Getreuer's mtetris.m, http://www.mathworks.com), based on the original game by Pajtnov in 1985. The original Tetris theme A was played repetitively during practice.

The blocks could be manipulated sideways (left and right arrows), rotated by 90 degrees (upright arrow) and dropped faster (downward arrow). Every game started at the same difficulty level but as the game progressed and the level increased, the blocks fell faster. The score increased by 5 points for each played block, and by 100, 250, 450 and 700 points respectively for completing a single, double, triple or quadruple line. Full rows disappeared and the rows above it moved down. When 10 lines were completed, the difficulty level increased and the blocks started falling faster. Game over was achieved when the stack of blocks reached the top of the playing field.

In order to discard Tetris experts, the score achieved at the end of the first training session could not exceed a fixed maximum (namely, 9500). Volunteers played Tetris during practice sessions of 2 hours, consisting of eight 15 minute blocks. This schedule resulted in a total of 6 hours of practice over 3 consecutive days for the experimental group. After each 15 minute block, performance scores of the completed Tetris games were automatically registered, resulting in 8 datasets per person per day. Performance scores include the number of points at the end of each game, how many single/double/triple/quadruple lines completed, how many blocks needed to complete one line, and the number of key presses to rotate a new block in the correct position.

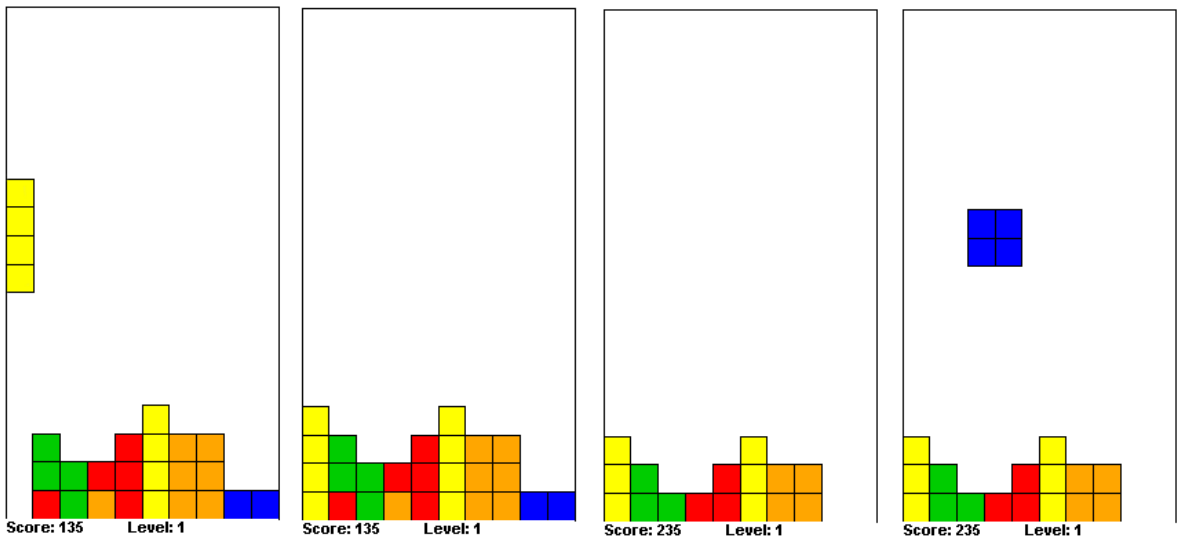


Figure 12. The computer game Tetris in progress from left to right, as used in this study. Volunteers have to manipulate the orientation of the falling tetrominoes to obtain solid rows of blocks without gaps. Solid rows of blocks disappear and the rows above this line each move down one row.

#### 3.2.3.4. Awakenings

During the nap, volunteers were monitored online with polysomnography (see 3.2.4 for details) and repetitively woken up by an auditory stimulus delivered 15, 45, 75, 120 or 180 seconds after the onset of sleep stage 1, in a pseudorandom order (see Figure 53 and following figures in annex 6.1 for examples of the online monitoring). On each awaking, volunteers were instructed to report their level of sleepiness according to the KSS and any *"thoughts, images, feelings, sensations or anything else going through their mind"*. All verbal reports were recorded. According to the sleep stage at the moment of the report, several conditions were possible:

- If S1 latency exceeded 10 minutes, a wake report was requested 10 minutes after the last report.
- If subjects woke up spontaneously within the last seconds of the foreseen interval, a wake report was asked.
- If they descended to sleep stage 2 within the foreseen interval, they received the auditory wake-up stimulus at the planned interval. If they woke up and reported, the

experiment was continued. However, if they did not wake up to report their mental content within 30 seconds, a new auditory stimulus was sent immediately. If this new auditory stimulus was still insufficient, the experimenter went into the room to wake up the participant.

### 3.2.4. Polysomnography

#### 3.2.4.1. Methodological considerations

Polysomnography (PSG) is a multiparametric test used in sleep studies, measuring brain activity with *electroencephalography*, EEG (Davis et al, 1937; Loomis et al, 1937a; Loomis et al, 1937b; Roth, 1961), horizontal and vertical eye movements with electrooculography, EOG (Dement and Kleitman, 1957a), and muscle activity with electromyography, EMG (Foulkes and Vogel, 1965).

*Electroencephalography* is a recording of electrical activity along the scalp, based on voltage fluctuations resulting from ionic current flows caused by neuronal activity (Baillet et al, 2001). A high sampling rate (in the order of milliseconds) allows for an accurate recording of high frequency brain oscillations. Scalp EEG activity shows oscillations at a variety of signals, with frequencies and spatial distributions that are characteristic for the different sleep-wake states. A typical adult human scalp EEG signal has amplitudes of about 10 to 100 μV.

For our basic sleep EEG (Rechtschaffen and Kales, 1968; Iber et al, 2007), we located 13 electrodes according to the 10-20 system, an internationally recognized method to apply scalp EEG electrodes to ensure standardized reproducibility over time and over subjects (Figure 13) (Niedermeyer and da Silva, 2004). We used Fz, Cz, Pz and Oz, referenced to the mean of A1 and A2, vertical and horizontal EOG, chin EMG, and a ground electrode on the midline of the forehead. The EEG allows us to detect K-complexes which are prominent on frontal areas (Happe et al, 2002), sleep spindles which predominate on the midline, and occipital alpha rhythm which wanes away at sleep onset.

We applied a four-channel EOG. Two electrodes to detect horizontal eye movements were placed 1cm lateral to the outer cantus of both eyes, and two electrodes for vertical movements were placed infraorbital and supraorbital (Rechtschaffen and Kales, 1968), allowing the detection of horizontal movements of both eyes and vertical movements of one eye. The EOG helps to detect wakefulness (saccades), the beginning of sleep stage 1 (slow rolling eye movements (SEM) in the range of 0.25-0.5Hz, mainly horizontally), sleep stage 2 (disappearance of SEMs) and rapid eye movement sleep (REM sleep, brusque movements in all directions).

For the EMG, we used two chin electrodes to detect muscle relaxation while drowsing off, and further relaxation or paralyzation to determine REM episodes.

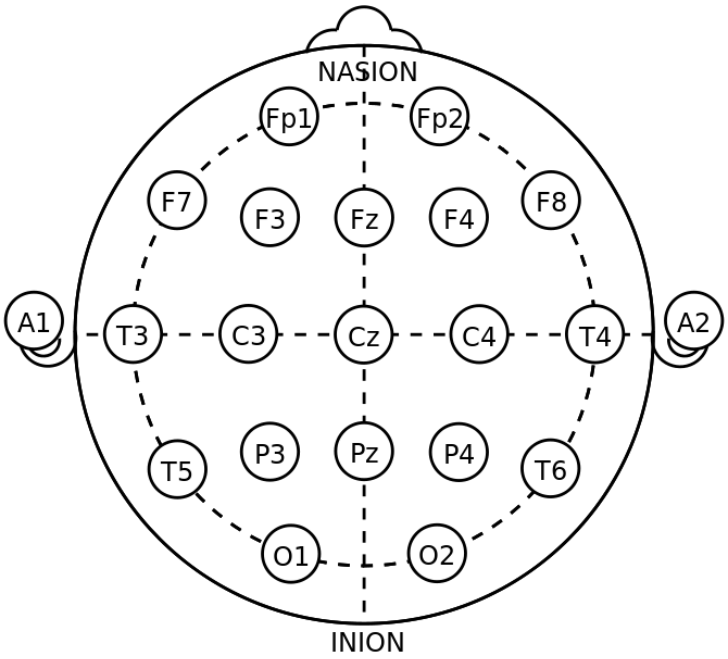


Figure 13. Locations of EEG scalp electrodes according to the 10-20 system. The 10 and 20 refer to the distances between electrodes: either 10% or 20% of the total front–back or right–left distance of the skull. Two anatomical landmarks are used for positioning the electrodes: the nasion and the inion. Each electrode has a letter to identify the lobe and a number to identify the hemisphere location. F, T, C, P and O stand for frontal, temporal, central, parietal, and occipital lobes, respectively. A, Pg and Fp identify the earlobes, nasopharyngeal and frontal polar sites. Z (zero) refers to an electrode placed on the midline; even numbers refer to the right hemisphere, whereas odd numbers refer to the left hemisphere.

Data were amplified and digitized using a V-Amp 16 (Brain Products GmbH, Gilching, Germany) using a 250 Hz sampling frequency and a band pass from DC (0 Hz) to Nyquist frequency (125 Hz). The useful frequency was filtered between the thresholds of 0,05 Hz and 125 Hz to avoid non-physiological measurements. All electrodes were filled with conductive electrode paste (EC2 Electrode Cream, Grass Technologies) and secured to the skin on the skull with Gauze (Mölnlycke Health Care), and on the face with elastic adhesive tape (Fixomull Stretch, BSN Medical) after preparing the scalp by light abrasion to reduce impedance due to dead skin cells. Electrode impedances were checked before the subject retired and if an electrode gave a reading above 5 kOhm it was re-applied. Electrodes that lost contact during the nap were not used for analysis. The quality of the PSG recordings was evaluated by horizontal and vertical eye movements, which are easy to recognize with eyes open, and by occipital alpha rhythm which appears immediately at the closure of the eyes. To evaluate the EMG quality, subjects had to open and close their mouth.

### 3.2.4.2. Sleep scoring of the naps

In this chapter, we explain how we detected the different vigilance stages. Example recordings of our study can be found in Figure 14 and all figures in annex 6.1.

PSG data was filtered during display using a fourth-order Butterworth filter: EEG between 0.1 and 20 Hz, EOG between 0.1 and 5 Hz, EMG between 10 and 125 Hz, and scored following standardized criteria in sequential epochs of 20 seconds (Rechtschaffen and Kales, 1968). The data was later analyzed offline using the FASST toolbox (http://www.montefiore.ulg.ac.be/~phillips/FASST.html; (Leclercq et al, 2011)).

**Wakefulness**

In the alert wake state with eyes opened, beta waves with a minimum frequency of 12 Hz and fast ample eye movements occur and muscle tension is high. However, in the relaxed wake state with eyes closed, alpha waves in the range of 8-12 Hz are dominant in the occipital lobe and eye movements (blinks and saccades) show decreased amplitudes (Figure 54).

**Sleep stage 1**

This is our state of interest. On EEG recordings, occipital alpha waves show a decreased rhythm and a fragmented pattern (Figure 55), leading to a progressive disappearance of the alpha waves (Hasan and Broughton, 1994) whilst central theta waves in the range of 4-7 Hz occur. The presence of vertex sharp waves is also possible (Figure 56): the waveform of these large amplitude waves is similar to that of K-complexes, but vertex waves are faster (in the range of 4-5 Hz) and have lower amplitudes (less than 75 μV). Slow rolling eye movements (SEMs) in the range of 0,25-0,5 Hz occur mainly in the horizontal direction (Figure 55, Figure 56, Figure 57, Figure 58) (Aserinsky and Kleitman, 1953, 1955; Hiroshige, 1998). Generally, muscle tonus slowly decreases in stage 1 sleep, while muscle twitches (Symonds, 1953; Coleman et al, 1980) can occur and can eventually lead to an arousal.

**Sleep stage 2**

The beginning of sleep is represented by the first epoch of stage 2 sleep (Rechtschaffen and Kales, 1968), when the K-complexes, less than 1 Hz and with a high amplitude of more than 100μV, and 11-15 Hz sleep spindles appear. From 20 to 50% of the waveforms are slow delta waves in the range of 0,5-4 Hz. Muscle activity decreases, and eye movements disappear (Figure 59, Figure 60).

**Sleep stage 3 and 4**

Although we recorded very few subjects in deep sleep, as they were usually awoken in light sleep, we show an example of stage 3 and 4 for the sake of completeness. Stage 3 and stage 4 sleep are referred to as slow wave sleep (Figure 61), because slow delta waves of 0,5-4Hz are dominant (Iber et al, 2007).

**REM sleep**

Rapid eye movement sleep is the sleep stage in which vivid dreams occur. EEG recordings resemble the relaxed wake state, with low amplitude fast waveforms. Sawtooth waves are also likely to occur. Rapid, brusque and binocularly symmetrical eye movements (saccades) are characteristic of this stage of sleep (Aserinsky and Kleitman, 1953, 1955; Dement and Kleitman, 1957b) (Figure 62). Also, muscle activity is decreased to an absolute minimum, due to a nearly complete muscular atonia.

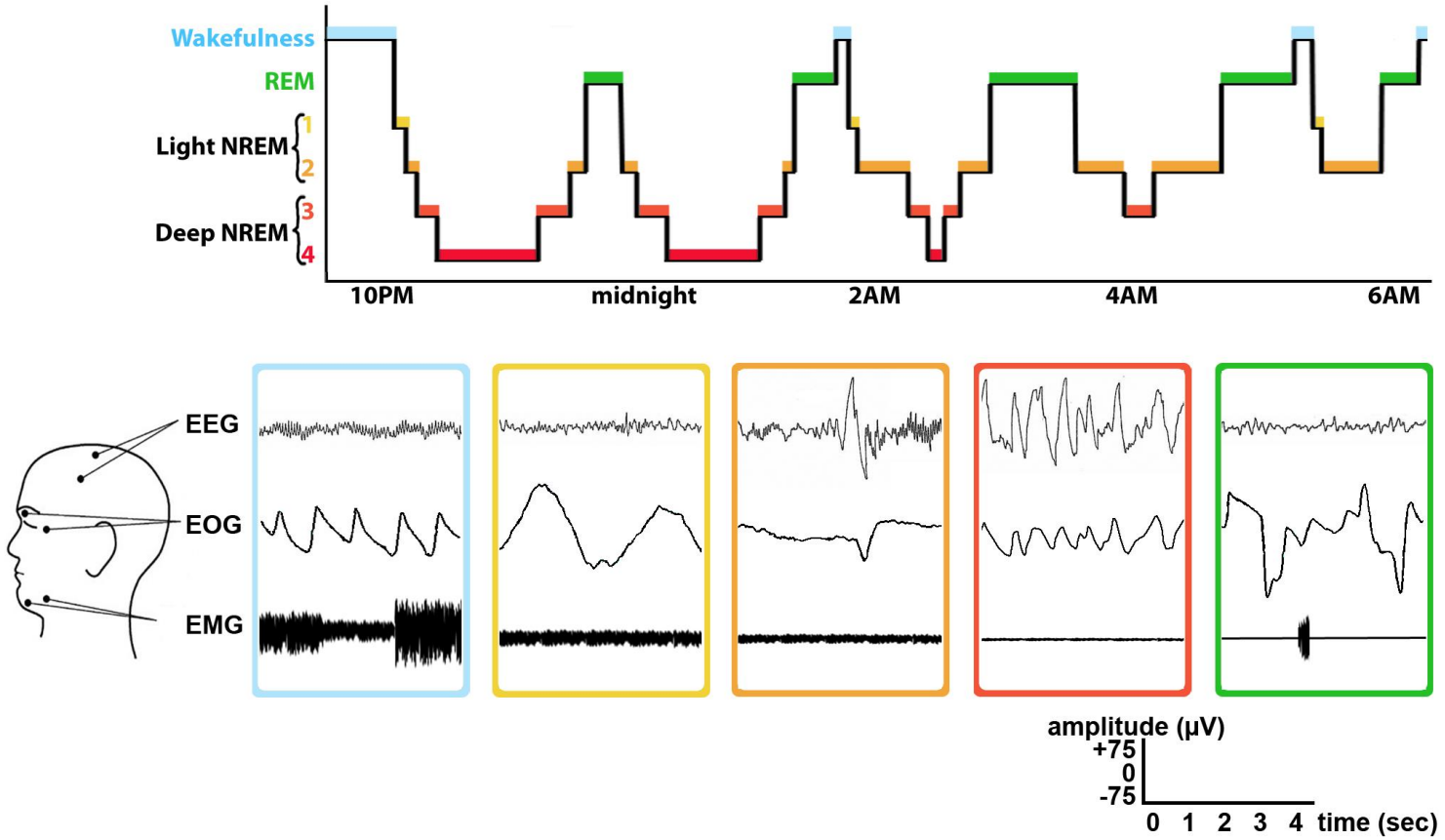


Figure 14. Polysomnography in different sleep stages during a normal night's sleep. In the relaxed wake state, alpha waves (8-12Hz) occur bilaterally in the posterior areas upon closure of the eyes. During sleep stage 1, alpha waves are fragmented and theta waves in the range of 4-7Hz predominate in the central part of the brain. Technically, the subject sleeps when stage 2 begins and sleep spindles in the range of 11-15Hz predominate over central leads and K-complexes of less than 1 Hz occur on frontal regions. During stage 3 and 4, also referred to as deep slow wave sleep, delta waves in the range of 0,5-4 Hz dominate the EEG recording and even have an overshoot to the EOG recording. During REM sleep, fast jerky eye movements, a low-voltage EEG pattern and a very low muscle tone are characteristic. Example recordings taken from our study).

### 3.2.5. Data analysis

#### 3.2.5.1. Content of the sleep-onset reports

Sleep-onset reports consisted of the level of sleepiness according to the KSS and the mental content at that particular moment. The content of all reports was classified according to whether it was related or not to Tetris. If related to Tetris, it was further categorized according to the nature of hypnagogic hallucinations (visual, auditory, kinesthetic imagery of Tetris, thoughts of Tetris, emotions related to Tetris, other games related to Tetris). Reports containing multiple themes could be assigned to multiple categories. The following categories were considered as **directly** related to Tetris:

- **Visual imagery of Tetris.** These include all reports in which the subject explicitly mentioned seeing elements of the Tetris game. The reports could be exclusively visual (unimodal) or mix elements of various modalities (multimodal). Example: "*And I was just seeing the game in my head and I had the impression that I was really playing […] It was just a mental image in which I saw blocks falling.*"

- **Auditory imagery of Tetris.** These reports contain sounds of Tetris with or without other mental representations and could be uni- or multimodal. Examples of both types: "*I've still been thinking about the Tetris music and uh… That's it, yes.*" or "*I had the music of Tetris in my mind, but at the same time I was thinking about other things with the music as background.*"

- **Tetris-related kinesthetic hallucinations.** These include bodily feelings and kinesthetic content related to the position and weight of the body, movements of the muscles, tendons and joints clearly related to Tetris practice. Example: *"I've got the impression of feeling heartbeats… I don't know very well... in a cubic place with blue tatamis on the ground."*

- **Thoughts about Tetris.** These are typically thoughts about the score achieved at Tetris. Example: "*I've been thinking about the scores I have achieved at Tetris.*"

- **Emotions related to Tetris.** These can consist of any primary emotion (anger, fear, sadness, disgust, surprise, anticipation, trust, and joy) or any of their combinations (excitement, curiosity, happiness, boredom, frustration, disappointment, etc.). Example: "*That one with four blocks, that orange one […] always when you need that block in one direction, you get a block in the different direction. That's very irritating*."

The following categories were considered as being **indirectly** related to Tetris practice:

- **Visual imagery of elements with spatial arrangements or movements characteristic of Tetris.** These elements are ordered as Tetris blocks and can include any kind of object such as boxes, bottles, cars, circles, crosses, beds, curtains, beehives with honeycombs, pieces of wood, snakes, eggs, balls, snow, etc. Example: "*I was ordering everything that is in my wardrobe. I have put everything in shoe boxes, but in my dream there were other shoe boxes. […] In my dream the shoe boxes were of different colors."*

- **Auditory imagery of melodies explicitly related to the Tetris theme.** These melodies are different from that of the Tetris game, and are not heard during the practice sessions. However, the volunteer explicitly claims that they are induced by the Tetris theme. Example: " *I was hearing the music 'Nous aimons vivre au fond des bois'. […] I think it's the same music as the Tetris game in fact. But, but it's instrumental music in fact.*" It should be noted that both the Tetris melody and the song 'Nous aimons vivre au fond des bois' are Russian folk songs, and their melodies are indeed quite similar.

- **Images, sounds, thoughts or emotions of another game, with a mention to Tetris.** These include reports about games with a goal similar to that of Tetris: video games (e.g. Pac-man), TV games (e.g. word games and quizzes) and party games (e.g, chess, downfall, connect four, battleship, card games, dice, etc.). Example: "*I was thinking about Tetris, and I was also thinking about a game, downfall, in which you have to turn and align four disks of the same color*."

Finally, three further classes of hallucinations were **not** considered as related to Tetris:

- **Images, sounds, thoughts or emotions related to the experimental settings, tasks or questionnaires or sleep-related concerns.** These include all reports about the PVT, scales, sleeping or sleep stages, beds, clocks, monitoring, actigraphy, questionnaires, the experimental room, the laboratory, the experimenter, the announcement of the experiment, the informed consent, etc. Although not related to the practice of Tetris, they are obviously related to the experiment. Example: "*A blurred image about someone who talks about his sleep*."

- **Content not related to Tetris.** This category is a very broad one which includes all reports which could not be assigned to any of the previous categories. These reports consist of images, sounds, thoughts or emotions without explicit relationship with Tetris. They also include references to games other than Tetris when the subject mentioned having played the game recently. Example: "*I was thinking of a game of chess I've been playing with a friend Tuesday evening*."

- **Nothing in mind, forgotten content.** As hypnagogic hallucinations tend to disappear immediately when they are focused on, it was expected that subjects often would forget their mental content. For instance, sometimes they just mentioned the KSS score, said they had nothing going on in their mind, or mentioned they had forgotten their mental content. Example: *"It's really very blurred, I don't know anymore*."

Sleep-onset reports were given scores by three independent judges, blind to the experimental conditions, performance data and time of the recording. Only those reports which 1) were assigned the same score by all three judges; 2) were obtained during the predefined sleep durations of 15, 45, 75, 120 or 180 seconds after S1 onset; 3) could be fully transcribed; and 4) contained at least one spoken word, were included in statistical analyses.

Thematic consistency was defined by the recurrence of similar images in several reports of the same volunteer,

either across awakenings within a single experimental day or across days. For instance, one volunteer reported "*I've been thinking about Tetris, about the green blocks and uhm it's difficult to place them correctly.*" and 40 minutes later he reported "*I've been thinking about the Tetris game, how to complete a line.*"

#### 3.2.5.2. Software and statistical testing

Statistical analyses were conducted with SPSS 16.0. As a rule, nonparametric tests were preferred given the small sample sizes: Kruskal Wallis and post hoc Mann Whitney U tests for between-group comparisons, Friedman and post hoc Wilcoxon Matched Pairs tests within the experimental group, Spearman's Bivariate Correlation tests for calculating correlations. Otherwise, parametric tests were considered when applicable (Tetris performance, alertness): Repeated Measures Analysis of Variance (RM-ANOVA) and post hoc Least Significant Differences (LSD).

## 3.3. Results

### 3.3.1. Population

A total of 43 volunteers aged between 18 and 33 years were assigned in the Tetris (n=16; 8 female), control (n=13; 8 female) and anticipation group (n=14; 6 female). Volunteers who deviated for more than 15minutes from their habitual sleep-wake schedule were excluded (see Figure 15 for an example of actigraphic data). Kruskal Wallis tests did not demonstrate any demographic difference between groups (Table 1).

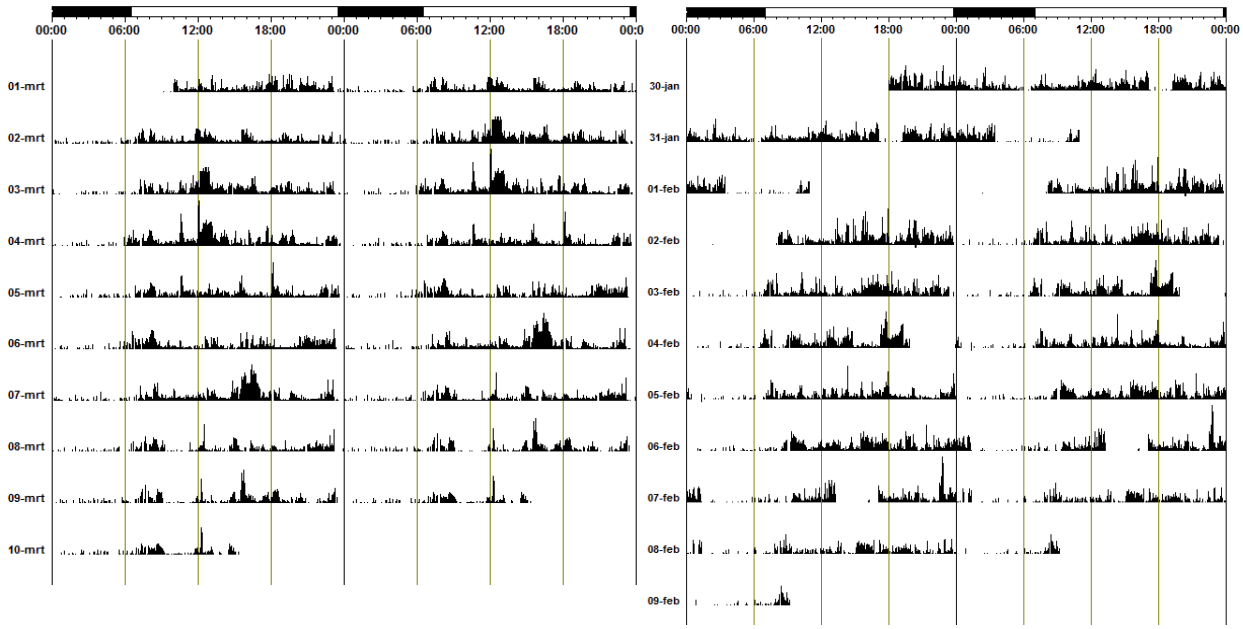


Figure 15 . Double plot of actigraphic data showing a regular sleep-wake rhythm (left) and an irregular sleep rhythm corresponding to an exclusion from the study (right). Collected data were averaged in time intervals of 1:00 minute. The vertical bar indicates the level of activity at any given time point.

### 3.3.2. Sleep-onset mentation reports

#### 3.3.2.1. Database

Out of a grand total of 1460 reports, the scorers agreed in 1246 reports, corresponding to an inter-rater reliability of 85%. Out of these 1246 included reports, 949 were collected during the predefined intervals of 15, 45, 75, 120 or 180 seconds after the onset of sleep stage 1. Among the 949 reports, 704 usable reports which could be fully transcribed and contained at least one spoken word were included in statistical analyses (Table 2 and Table 3).

#### 3.3.2.2. Group differences

Sleep-onset mentation during the first day of the experiment was compared between groups (Table 2). They did not significantly differ in the overall capacity to recall mental content at sleep onset (145 usable reports in the Tetris group out of 195 recorded on the first day; 107 out of 151 in the control group; 112 out of 151 in the anticipation group; Kruskal Wallis $\chi^2$=0.626, df=2; p=0.731).

By contrast, the number of Tetris-related reports differed significantly between groups (Kruskal Wallis $\chi^2$=10.332,

df=2; p=0.006). In the experimental group, 13 out of 145 reports were related to Tetris. On the other hand, in the control group, 1 usable report out of 107 was scored as Tetris-related while in the anticipation group there were 3 Tetris-related reports out of 112 usable reports (Table 2 and Figure 16). Post hoc Mann Whitney tests revealed that Tetris-related reports were significantly more frequent in the Tetris than in the control group (U=7134.5; p=0.006) and anticipation group (U=7609.5; p=0.039). No significant difference could be found between the control and anticipation group (U=5887.5; p=0.336).

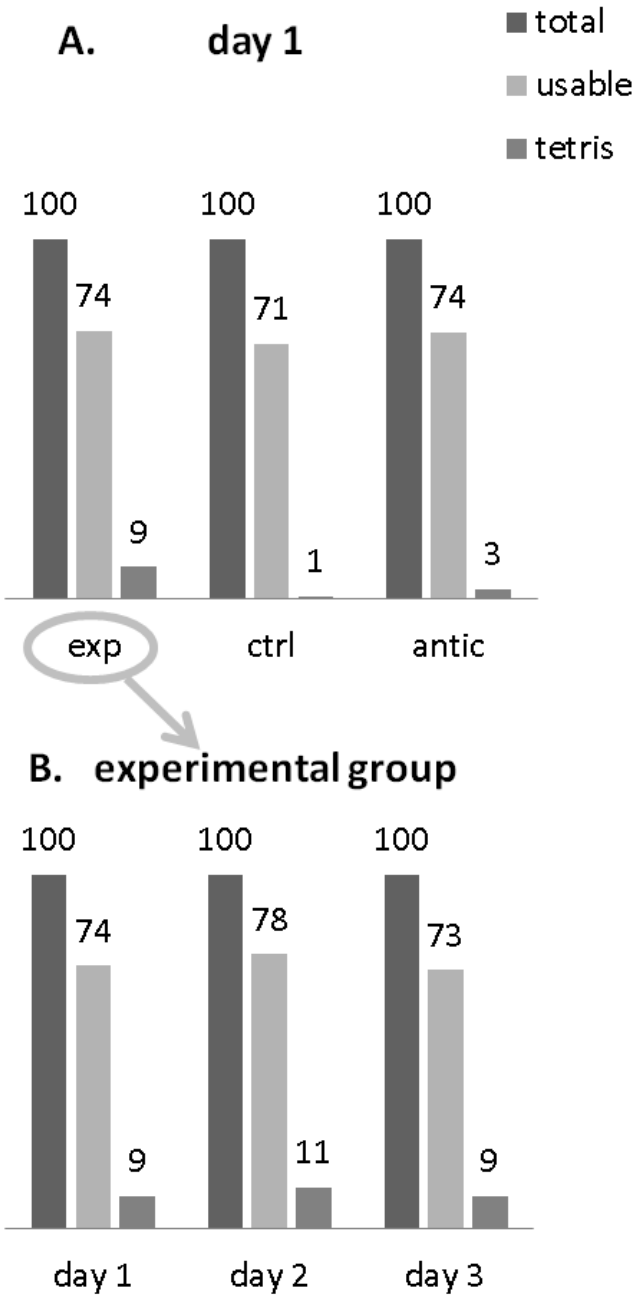


Figure 16. Percentages of usable (dark gray) and tetris-related (lighter gray) mentation reports. a. The first day in experimental, control and anticipation group. b. The first, second and third day in the experimental group.

Table 1. Demographic data. Median and range (minimum and maximum) is shown for each group. Kruskal Wallis tests did not show any difference between the experimental groups (p>0.05 for all parameters). Med: median; min: minimum; max: maximum; SMP: Sleep midpoint; PSQI: Pittsburgh sleep quality index; LSDQ: London sleep and dreaminess questionnaire

| | Tetris group | | | control group | | | anticipation group | | | Kruskal Wallis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **med** | **min** | **max** | **med** | **min** | **max** | **med** | **min** | **max** | **$\chi^2$** | **df** | **p** |
| **sex** | | | | | | | | | | 0.933 | 2 | 0.627 |
| **SMP** | 3:37 | 3:00 | 4:30 | 3:15 | 2:45 | 7:00 | 3:30 | 1:30 | 7:00 | 0.210 | 2 | 0.900 |
| **age** | 22 | 18 | 28 | 23 | 18 | 26 | 25 | 19 | 33 | 5.882 | 2 | 0.053 |
| **Epworth** | 5 | 0 | 9 | 3 | 0 | 12 | 5 | 1 | 11 | 2.368 | 2 | 0.306 |
| **chronotype** | 54 | 43 | 62 | 55 | 40 | 61 | 51.5 | 39 | 66 | 1.185 | 2 | 0.553 |
| **PSQI** | 3 | 1 | 5 | 3 | 1 | 6 | 4 | 1 | 6 | 4.470 | 2 | 0.107 |
| **anxiety** | 2.5 | 0 | 6 | 3 | 0 | 8 | 2 | 0 | 14 | 0.899 | 2 | 0.638 |
| **depression** | 2 | 0 | 7 | 2 | 0 | 10 | 2.5 | 0 | 9 | 1.527 | 2 | 0.466 |
| **LSDQ** | 93.5 | 72 | 104 | 87 | 68 | 141 | 86 | 6 | 141 | 2.745 | 2 | 0.253 |

Table 2. Content of sleep-onset mentation reports of day 1, in Tetris (N=16), control (N=13) and anticipation (N=14) groups. The total number of included reports is shown for each category (i.e. attributed the same score by the three judges and recorded during the defined intervals), the number of usable reports (i.e. containing at least one spoken word and which could be fully transcribed) and the number of usable reports related to Tetris. Also, the number of volunteers contributing to these totals is shown. Interval length since the onset of sleep stage 1 is a mutually exclusive category, as well as classification into vigilance stages. However, reports could be assigned in multiple sensory classes.

| **day 1** | | **Tetris group** | | | | | | **control group** | | | | | | **anticipation group** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **total** | | **usable** | | **Tetris** | | **total** | | **usable** | | **Tetris** | | **total** | | **usable** | | **Tetris** | |
| | | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** |
| **day** | **1** | 195 | 16 | 145 | 16 | 13 | 7 | 151 | 13 | 107 | 13 | 1 | 1 | 151 | 14 | 112 | 14 | 3 | 3 |
| **interval** | **15** | 45 | 16 | 34 | 15 | 2 | 2 | 29 | 13 | 24 | 13 | 0 | 0 | 28 | 13 | 23 | 12 | 0 | 0 |
| | **45** | 35 | 15 | 27 | 14 | 0 | 0 | 31 | 13 | 18 | 12 | 0 | 0 | 31 | 12 | 25 | 12 | 0 | 0 |
| | **75** | 40 | 16 | 30 | 15 | 2 | 2 | 34 | 13 | 25 | 13 | 0 | 0 | 31 | 14 | 21 | 11 | 0 | 0 |
| | **120** | 39 | 14 | 31 | 14 | 7 | 5 | 28 | 13 | 21 | 10 | 1 | 1 | 31 | 13 | 22 | 12 | 1 | 1 |
| | **180** | 36 | 14 | 23 | 13 | 2 | 2 | 29 | 12 | 19 | 11 | 0 | 0 | 30 | 13 | 21 | 11 | 2 | 2 |
| **stage** | **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 3 | 1 | 0 | 0 |
| | **1** | 141 | 16 | 109 | 16 | 10 | 6 | 113 | 13 | 83 | 13 | 1 | 1 | 115 | 14 | 88 | 14 | 1 | 1 |
| | **2** | 53 | 11 | 35 | 15 | 3 | 3 | 36 | 10 | 23 | 9 | 0 | 0 | 31 | 8 | 21 | 7 | 2 | 2 |
| | **3** | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 2 | 1 | 1 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 |
| **class** | **image** | 48 | 12 | 28 | 12 | 12 | 7 | 37 | 11 | 19 | 8 | 1 | 1 | 56 | 11 | 38 | 9 | 2 | 2 |
| | **sound** | 15 | 9 | 9 | 6 | 2 | 1 | 6 | 6 | 1 | 1 | 0 | 0 | 12 | 7 | 6 | 5 | 0 | 0 |
| | **thought** | 21 | 9 | 11 | 6 | 0 | 0 | 21 | 10 | 17 | 8 | 0 | 0 | 30 | 11 | 16 | 8 | 1 | 1 |
| | **emotion** | 1 | 1 | 0 | 0 | 0 | 0 | 3 | 2 | 2 | 1 | 0 | 0 | 12 | 5 | 10 | 5 | 0 | 0 |
| | **kinesthetic** | 1 | 1 | 1 | 1 | 0 | 0 | 3 | 3 | 1 | 1 | 0 | 0 | 14 | 7 | 8 | 5 | 1 | 1 |

Table 3. Content of sleep-onset mentation reports across days within the experimental Tetris group. The total number of included reports is shown for each category (i.e. attributed the same score by the three judges and recorded during the defined intervals), the number of usable reports (i.e. containing at least one spoken word and which could be fully transcribed) and the number of usable reports related to Tetris. Also, the number of volunteers contributing to these totals is shown. Interval length since the onset of sleep stage 1 is a mutually exclusive category, as well as classification into vigilance stages. However, reports could be assigned in multiple sensory classes.

| **Tetris group** | | **day 1** | | | | | | **day 2** | | | | | | **day 3** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **total** | | **usable** | | **Tetris** | | **total** | | **usable** | | **Tetris** | | **total** | | **usable** | | **Tetris** | |
| | | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** | **reports** | **subjects** |
| **day** | | 195 | 16 | 145 | 16 | 13 | 7 | 214 | 16 | 166 | 16 | 19 | 10 | 238 | 16 | 174 | 16 | 16 | 9 |
| **interval** | **15** | 45 | 16 | 34 | 15 | 2 | 2 | 41 | 15 | 36 | 13 | 2 | 2 | 55 | 16 | 39 | 15 | 6 | 5 |
| | **45** | 35 | 15 | 27 | 14 | 0 | 0 | 43 | 15 | 30 | 14 | 1 | 1 | 46 | 16 | 34 | 16 | 2 | 1 |
| | **75** | 40 | 16 | 30 | 15 | 2 | 2 | 39 | 16 | 28 | 13 | 6 | 5 | 43 | 16 | 35 | 15 | 2 | 2 |
| | **120** | 39 | 14 | 31 | 14 | 7 | 5 | 45 | 16 | 38 | 16 | 3 | 3 | 43 | 15 | 29 | 15 | 1 | 1 |
| | **180** | 36 | 14 | 23 | 13 | 2 | 2 | 46 | 16 | 34 | 16 | 7 | 6 | 51 | 16 | 37 | 13 | 5 | 4 |
| **stage** | **0** | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 2 | 2 | 0 | 0 | 2 | 2 | 2 | 2 | 0 | 0 |
| | **1** | 141 | 16 | 109 | 16 | 10 | 6 | 147 | 16 | 122 | 16 | 16 | 9 | 159 | 16 | 125 | 16 | 14 | 8 |
| | **2** | 53 | 11 | 35 | 11 | 3 | 3 | 64 | 14 | 42 | 13 | 3 | 3 | 77 | 15 | 47 | 15 | 2 | 2 |
| | **3** | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **class** | **image** | 48 | 12 | 28 | 12 | 12 | 7 | 59 | 16 | 39 | 16 | 17 | 10 | 64 | 14 | 38 | 14 | 14 | 8 |
| | **sound** | 15 | 9 | 9 | 6 | 2 | 1 | 18 | 9 | 8 | 6 | 2 | 2 | 18 | 9 | 4 | 3 | 0 | 0 |
| | **thought** | 21 | 9 | 11 | 6 | 0 | 0 | 20 | 8 | 18 | 8 | 1 | 1 | 18 | 10 | 12 | 7 | 2 | 2 |
| | **emotion** | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 3 | 2 | 1 | 1 | 1 | 1 |
| | **kinesthetic** | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

### 3.3.3. Effect of repeated training, interval and vigilance state

Within the Tetris group, Tetris-related hypnagogic hallucinations were reported by 13 of the 16 experimental subjects (Figure 17A and Table 3). Out of 485 usable reports across the three experimental days, 48 reports contained Tetris-related content, corresponding to a proportion of 10% of Tetris-related hypnagogic hallucinations after Tetris practice. Out of these 13 volunteers, 2 subjects reported one Tetris-related hallucination, 4 had two reports and 2 had three reports. Five further volunteers reported respectively four, five, six, eight and nine Tetris-related hallucinations (Figure 17A and Table 3).

The propensity to recall mental content at sleep onset did not significantly differ across days in the Tetris group (Friedman $\chi^2$=4.246; df=2; p=0.120). The rate of Tetris-related reports did neither significantly differ across days ($\chi^2$=1.542; df=2; p=0.463; Figure 17B) nor across intervals ($\chi^2$=6.912; df=4; p=0.141; Figure 17C). Out of the 48 task-related reports, 13 were obtained during the first day (13/48=27%), 19 during the second day (19/48=40%) and 16 during the third day (16/48=33%). A total of 10 reports was obtained after the interval of 15 sec (10/48=21%), 3 after 45 sec (3/48=6%), 10 after 75 sec (10/48=21%), 11 after 120 sec (11/48=23%) and 14 after 180 seconds after the onset of S1 (14/48=29%).

By contrast, the rate of Tetris-related reports significantly varied with respect to vigilance stage (Friedman $\chi^2$=25.727; df=3; p<0.001; Figure 17D). There were significantly more reports after awakening from stage 1 (40/356=11%) than stage 3 sleep (0/1=0%; post hoc Wilcoxon Signed Ranks p=0.001) and from stage 2 (8/124=6%) than stage 3 (p=0.018). Whenever present, sleep stage 3 was almost never associated with mental content. There were also more reports obtained following awakenings from sleep stage 1 (p=0.001) and stage 2 (p=0.018) than in the wake state (0/4=0%). No significant difference between sleep stage 1 and 2 could be found in this study (p=0.650).

The state of vigilance also significantly influenced the proportion of both indirect (33 out of 48 Tetris-related reports across all stages; Friedman $\chi^2$=27.690; df=3; p<0.001; Figure 17D gray) and direct incorporations (16 out of 48; $\chi^2$=12.000; df=3; p=0.007; Figure 17D black). Post hoc Wilcoxon tests confirmed significantly less indirect reports during wake (0/0) compared to stage 1 (25/41=61%; p=0.001) and stage 2 (8/8=100%; p=0.008) and less during stage 3 (0/0) than during stage 1 (p=0.001) and stage 2 (p=0.008). Again, no significant difference was found between stage 1 and stage 2 (p=0.112). Despite the significant overall effect of vigilance state on direct reports, none of the post hoc pairwise comparisons were significant.

### 3.3.4. Characterization of mental reports

The rate of Tetris-related reports varied significantly across sensory classes (Friedman $\chi^2$=31.141; df=4; p<0.001; Figure 17E). Relative to the number of usable reports in each sensory class, visual hallucinations (39/101=39%) occurred more frequently than auditory (4/21=19%; post hoc Wilcoxon p=0.009), thoughts (1/39=3%; p=0.019), emotions (1/2=50%; p=0.003), and kinesthetic reports (0/1=0%; p=0.001). Interestingly, indirect visual Tetris imagery (N=14) appeared as frequent as direct visual hallucinations of the original Tetris tetrominoes (N=13). Very few reports actually consisted of Tetris-related thoughts (N=3) or included an explicit emotional reference (N=1).

Thematic consistency in Tetris-related reports was infrequently reported, either over days (Figure 18A) or over successive awakenings during one day (Figure 18B). Over days, thematic consistency was observed in 6 volunteers out of 16 in the experimental group (subjects a-f, Figure 18A): 4 volunteers reported thematically consistent Tetris-related hallucinations on all three days (a-d) while 2 reported only the second and third day (e and f). Over repeated awakenings on a given day, 4 volunteers reported related Tetris content (subjects a,b,c,g; Figure 18B). Namely, on day one, the 13 Tetris reports were provided by 7 different subjects without any thematic persistency. On day two, the 19 Tetris hallucinations were reported by 10 different subjects of whom 3 subjects each had 2 related reports

(a,c,g). On day three, 16 Tetris hallucinations were provided by 9 different volunteers, 2 reporting each 2 consistent Tetris themes (b and c) and 1 reporting 3 consistent Tetris hallucinations (a). These reports were never consecutive: 3 to 11 unrelated reports (i.e. 6 to 26minutes) were interleaved between the reports having a consistent theme.

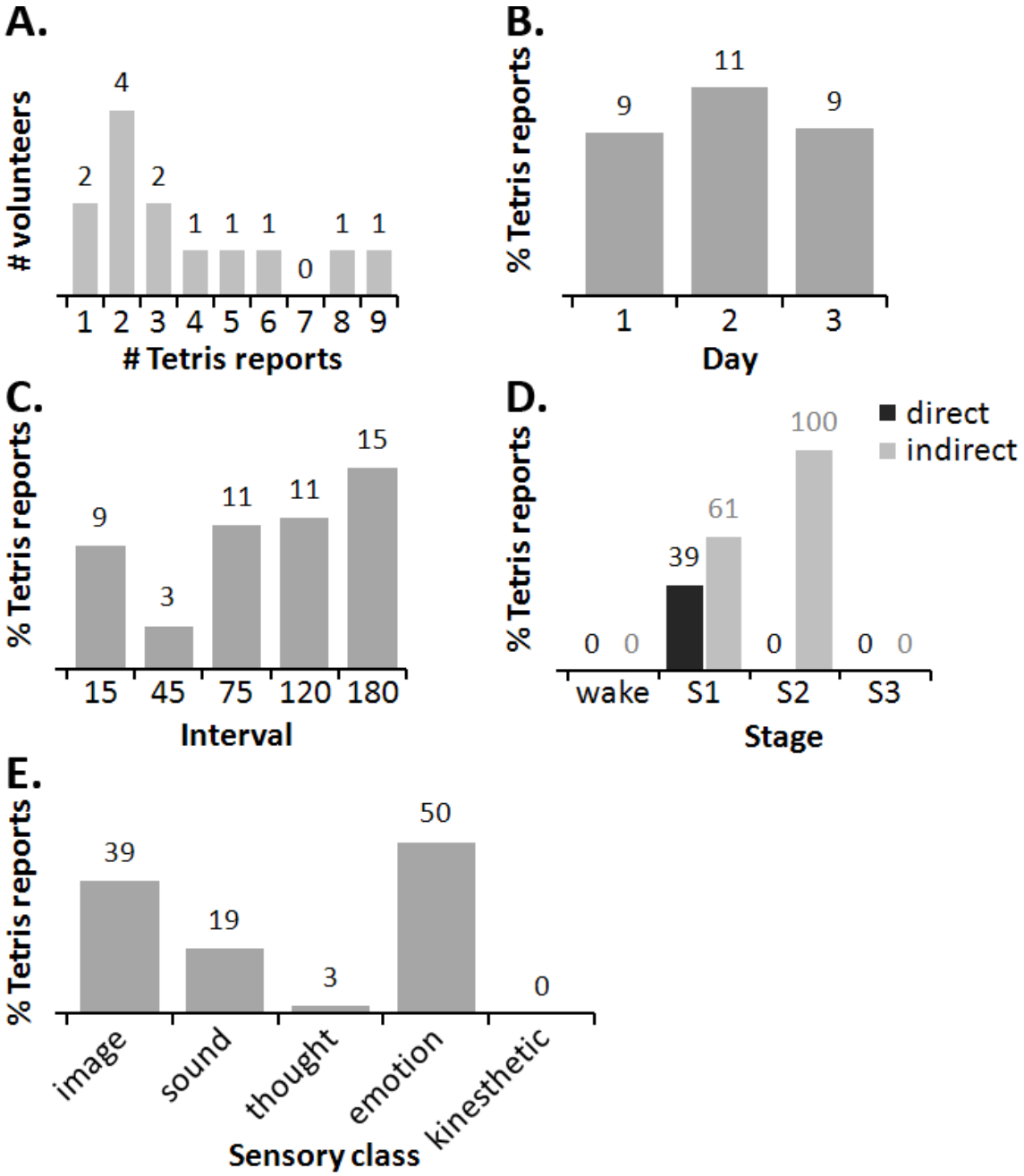


Figure 17. Content of Tetris-related sleep-onset reports in the Tetris group. (a) Contribution of individual subjects to the group total of Tetris-related sleep-onset mentation reports. (b–e) Percentage of Tetris-related sleep-onset reports relative to the number of usable reports of each category: (b) across days; (c) across interval since onset of S1; (d) according to sleep stage, separately for direct or indirect incorporations; and (e) according to sensory modality.

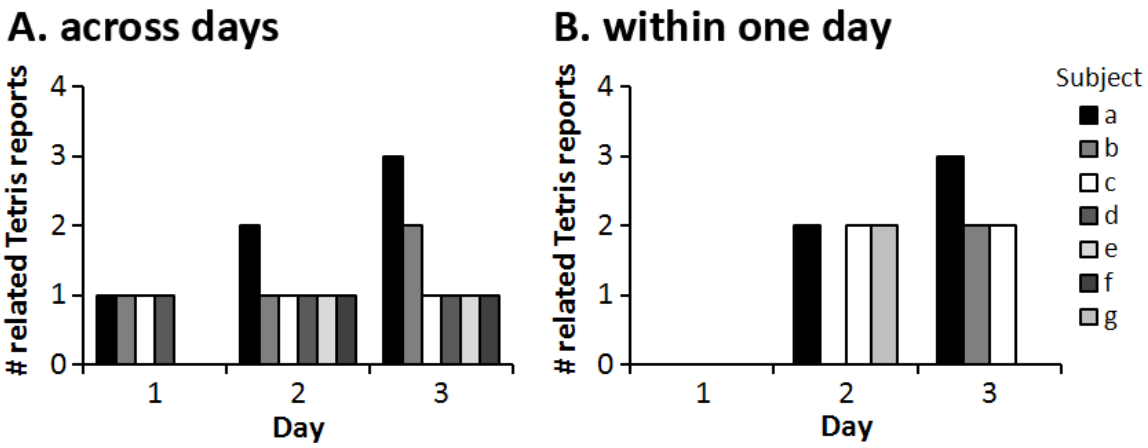


Figure 18. Thematic consistency of Tetris-related reports in the experimental group. (a) Across days; (b) over repeated awakenings during one particular day. The absolute number of Tetris-related reports with a consistent theme is shown for individual subjects.

### 3.3.5. Sleep-onset reports and performance

We examined whether sleep-onset Tetris-related reports were related to gaming performance. A RM-ANOVA showed no significant difference between the Tetris and anticipation group ($F(1)=0.435$; $p=0.515$) according to Tetris performance across training blocks. The learning curve was comparable in the two groups (no interaction group*block $F(7)=1.826$; $p=0.085$). Within the experimental group, a RM-ANOVA showed that Tetris performance changed across training blocks ($F(7)=2.417$; $p=0.025$) and across training days ($F(1.178)=9.945$; Greenhouse-Geisser $\varepsilon=0.589$; $p=0.004$) although there was no interaction between days and blocks ($F(14)=1.024$; $p=0.431$). Performance increased across training days (Figure 19A), as indicated by post hoc LSD tests showing a significant progression in performance between day 1 and 2 ($p=0.042$), between day 1 and 3 ($p=0.001$) and between day 2 and 3 ($p=0.002$).

KSS scores were inversely correlated with the Tetris gaming score achieved at that moment in the experimental group (Pearson's Correlation Coefficient = -0,128; two tailed significance = 0,001), suggesting that performance decreased with increasing sleepiness (Figure 20).

We did not find any significant correlation between the gain in performance across days and the rate of Tetris-related hypnagogic reports during post-training naps ($r=0.074$;

p=0.784). This result was expected because, by design, 'naps' actually consisted of iterative awakening from light sleep, which interrupted and perturbed the ongoing mental processes. Moreover, in contrast to Wamsley et al. (2010), we only observed a trend between initial Tetris score and the rate of Tetris-related mental report density at sleep onset (Spearman's Bivariate Correlation Coefficient r=0.488; two-tailed significance p=0.065). However, we found that the maximum individual Tetris scores are significantly related to the absolute number of Tetris-related sleep-onset reports (r=0.535, p=0.033; Figure 19B).

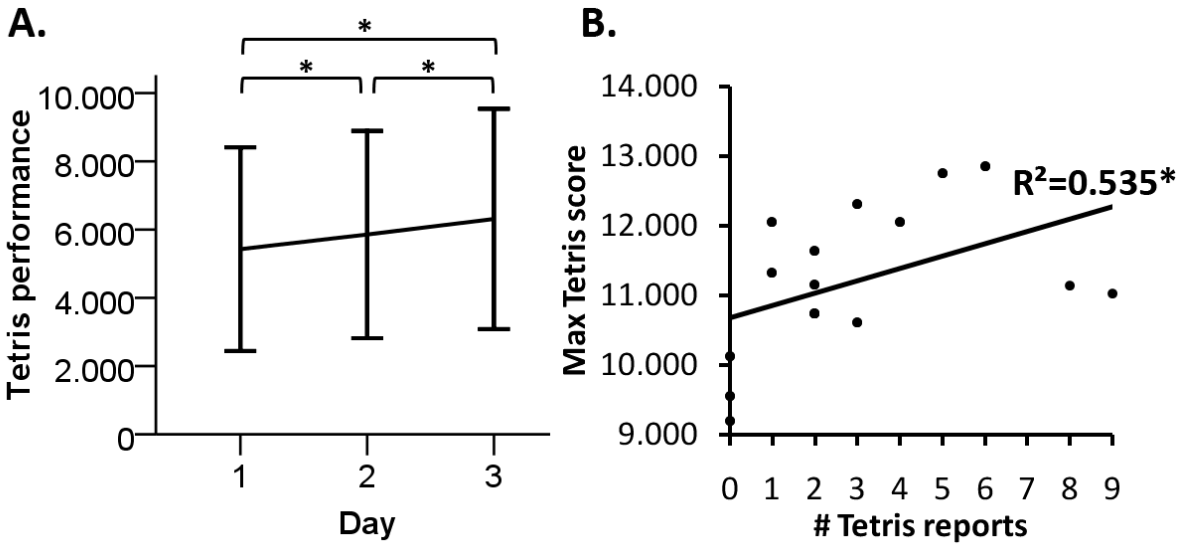


Figure 19 (a) Tetris performance scores (mean ± SD) across 3 days. Performance improved significantly across 3 days of practice. (b) Absolute number of Tetris-related sleep-onset reports in relation to Tetris performance. Each dot represents a participant. The number of reports was obtained by pooling all data of one subject across days, intervals and sleep stages. Tetris performance was measured as the maximal score obtained across 3 days of practice. The interpolation line shows a significant correlation (p = 0.033).

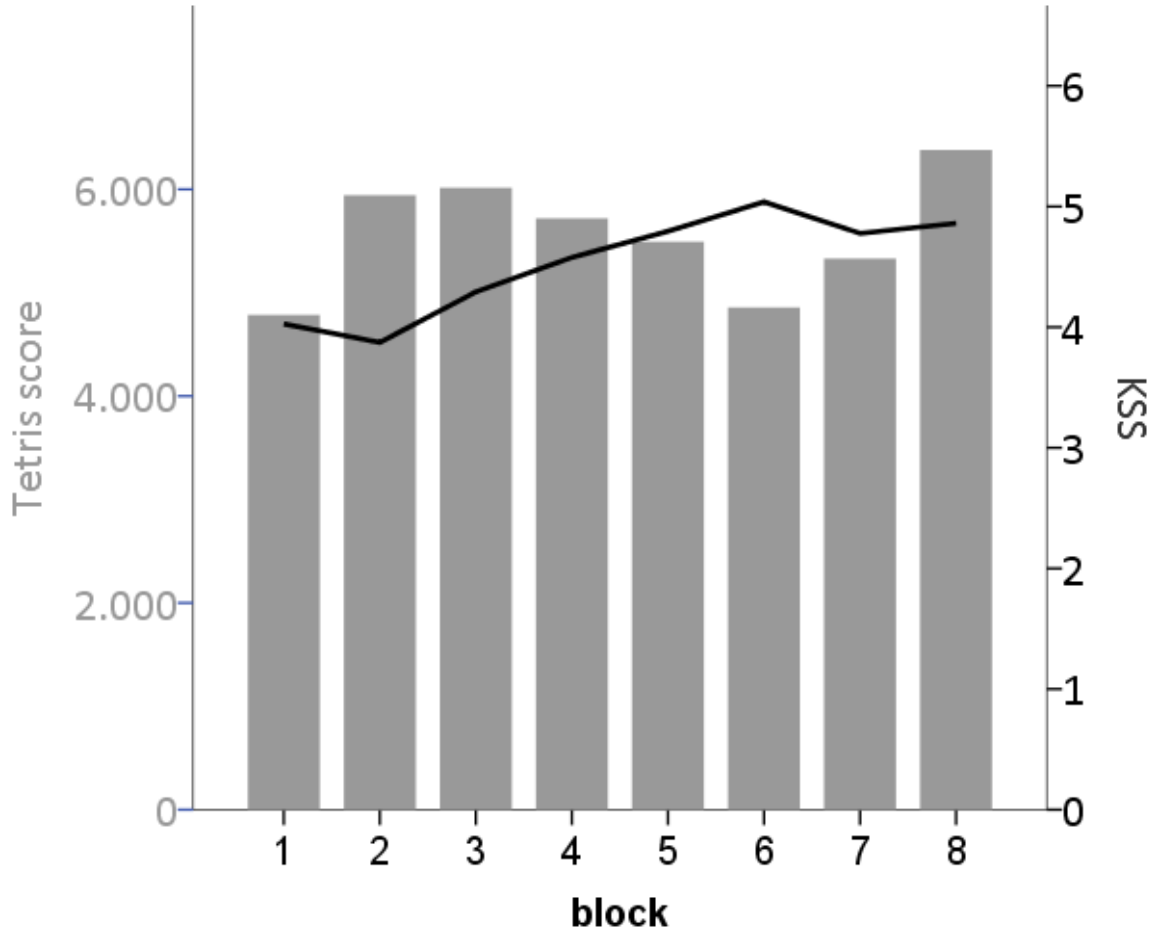


Figure 20. Tetris performance scores in the experimental group (gray blocks) and their corresponding level of alertness according to the KSS scale (black curve) across 15 minute blocks of practice show that performance is inversely correlated with level of alertness.

### 3.3.6. Alertness

The difference in content of sleep-onset reports between groups could not be attributed to difference in alertness. A RM-ANOVA showed that there was no difference between groups neither according to average reaction times during PVT ($F(2)=2.592$; $p=0.088$) nor KSS scores ($F(2)=0.351$; $p=0.706$) (Figure 21). Likewise, the RM-ANOVA across the three training days of the experimental group showed no significant effect of day on the PVT reaction times ($F(1.356)=0.068$; Greenhouse-Geisser $\varepsilon=0.678$; $p=0.867$).

Similarly, there was no significant difference in any sleep parameter that might account for the difference in content of sleep-onset reports between groups (Kruskal Wallis tests; $p>0.05$ for most parameters, Table 4) nor across days in the

Tetris group (Friedman tests; $p>0.05$ for most parameters, Table 5). These negative results were expected as the experimental design essentially relied on awakenings from sleep stage 1.

### 3.3.7. Content of hypnagogic hallucinations

The content of all reports was classified regarding relation to Tetris (see annex 6.2.1) and sensory class (see annex 6.2.2).

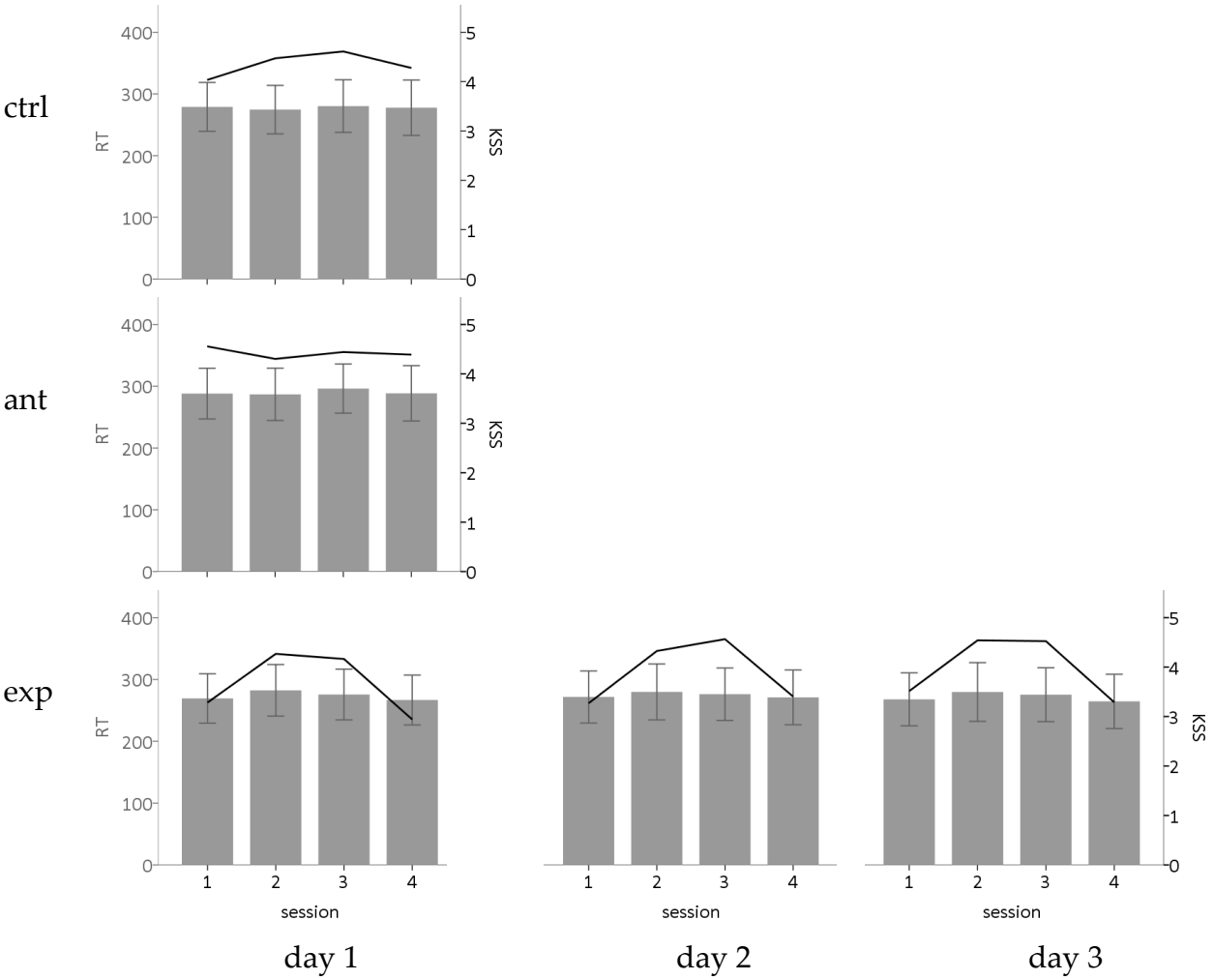


Figure 21. Mean PVT reaction times (in milliseconds) with its standard deviations, and mean KSS scores during the four sessions across the day of the control group (upper part), anticipation group (middle part) and experimental group (lower part) during the first, second and third day (left, middle and right panel respectively).

Table 4. Comparison of the sleep parameters for day 1 between experimental groups. Kruskal Wallis tests revealed no significant differences between groups (p>0.05 for most parameters). Time in each stage and latency (from lights off) is displayed in seconds. The time allowed to sleep is the total duration between lights off and lights on. The total sleep time represents only the sleep duration without wakefulness, movement and stage 1. n = number of included subjects in the Kruskal Wallis test; med = median; min = minimal value; max = maximal value. Latency of REM could not be computed due to a too small number of measurements.

| **day 1** | **Tetris group** | | | | **control group** | | | | **anticipation group** | | | | **Kruskal Wallis** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **med** | **min** | **max** | **n** | **med** | **min** | **max** | **n** | **med** | **min** | **max** | **$\chi^2$** | **df** | **p** |
| **time awake** | 16 | 2470 | 680 | 4340 | 13 | 2580 | 1180 | 3660 | 14 | 2920 | 2000 | 4320 | 3.679 | 2 | 0.159 |
| **time in S1** | 16 | 1580 | 480 | 2600 | 13 | 1860 | 1060 | 2500 | 14 | 1570 | 280 | 2560 | 0.705 | 2 | 0.703 |
| **time in S2** | 16 | 470 | 0 | 1460 | 13 | 500 | 0 | 880 | 14 | 20 | 0 | 900 | 7.145 | 2 | 0.028 |
| **time in S3** | 16 | 0 | 0 | 40 | 13 | 0 | 0 | 60 | 14 | 0 | 0 | 60 | 0.499 | 2 | 0.779 |
| **time in S4** | 16 | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 14 | 0 | 0 | 0 | 0.000 | 2 | 1.000 |
| **time in REM** | 16 | 0 | 0 | 80 | 13 | 0 | 0 | 0 | 14 | 0 | 0 | 0 | 1.688 | 2 | 0.430 |
| **movement time** | 16 | 300 | 0 | 1000 | 13 | 360 | 0 | 560 | 14 | 720 | 420 | 1240 | 16.204 | 2 | 0.000 |
| **latency S1** | 16 | 338.5 | 92 | 1140 | 13 | 526 | 137 | 1240 | 14 | 690 | 198 | 1400 | 9.204 | 2 | 0.010 |
| **latency S2** | 13 | 1980 | 572 | 3030 | 11 | 2337 | 317 | 4689 | 7 | 3380 | 942 | 4880 | 3.948 | 2 | 0.139 |
| **latency REM** | 1 | 1480 | 1480 | 1480 | | | | | | | | | | | |
| **time allowed to sleep** | 16 | 5066 | 3591 | 5750 | 13 | 4890 | 4160 | 6044 | 14 | 5542 | 4061 | 5863 | 0.008 | 2 | 0.008 |
| **total sleep time** | 16 | 480 | 0 | 1460 | 13 | 500 | 0 | 920 | 14 | 40 | 0 | 940 | 0.036 | 2 | 0.036 |

Table 5. Comparison of the sleep parameters within the Tetris group across the three days. Friedman tests revealed no significant differences between the three days (p>0.05 for most parameters). Time in each stage and latency (from lights off) is displayed in seconds. Latency for stage 1, 2 and REM is also displayed in seconds. The time allowed to sleep is the total duration between lights off and lights on. The total sleep time represents only the sleep duration without wakefulness, movement and stage 1. n = number of included subjects in the Friedman test; med = median; min = minimal value; max = maximal value. Latency of REM could not be computed due to a too small number of measurements.

| **Tetris group** | **day 1** | | | | **day 2** | | | | **day 3** | | | | **Friedman** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **med** | **min** | **max** | **n** | **med** | **min** | **max** | **n** | **med** | **min** | **max** | $\chi^2$ | **df** | **p** |
| **time awake** | 16 | 2470 | 680 | 4340 | 16 | 2320 | 560 | 3840 | 16 | 1910 | 540 | 4140 | 1.125 | 2 | 0.570 |
| **time in S1** | 16 | 1580 | 480 | 2600 | 16 | 1540 | 820 | 2660 | 16 | 1360 | 640 | 2840 | 0.125 | 2 | 0.939 |
| **time in S2** | 16 | 470 | 0 | 1460 | 16 | 590 | 0 | 2180 | 16 | 740 | 0 | 1640 | 8.414 | 2 | 0.015 |
| **time in S3** | 16 | 0 | 0 | 40 | 16 | 0 | 0 | 320 | 16 | 0 | 0 | 100 | 3.600 | 2 | 0.165 |
| **time in S4** | 16 | 0 | 0 | 0 | 16 | 0 | 0 | 100 | 16 | 0 | 0 | 0 | 2.000 | 2 | 0.368 |
| **time in REM** | 16 | 0 | 0 | 80 | 16 | 0 | 0 | 80 | 16 | 0 | 0 | 680 | 2.000 | 2 | 0.368 |
| **movement time** | 16 | 300 | 0 | 1000 | 16 | 340 | 0 | 920 | 16 | 500 | 0 | 1120 | 0.833 | 2 | 0.659 |
| **latency S1** | 16 | 338.5 | 92 | 1140 | 16 | 230 | 106 | 1021 | 16 | 193 | 75 | 1707 | 1.625 | 2 | 0.444 |
| **latency S2** | 13 | 1980 | 572 | 3030 | 13 | 1097 | 667 | 1864 | 15 | 1169 | 310 | 2527 | 4.167 | 2 | 0.125 |
| **latency REM** | 1 | 1480 | 1480 | 1480 | 3 | 1206 | 780 | 5020 | 2 | 1211 | 980 | 1442 | | | |
| **time allowed to sleep** | 16 | 5066 | 3591 | 5750 | 16 | 4933.5 | 3414 | 5405 | 16 | 5269 | 3474 | 5740 | 7.125 | 2 | 0.028 |
| **total sleep time** | 16 | 480 | 0 | 1460 | 16 | 630 | 0 | 2640 | 16 | 800 | 0 | 1680 | 8.742 | 2 | 0.013 |

## 3.4. Discussion

Our data show that it is possible to reliably induce stereotypical hypnagogic hallucinations of Tetris during daytime naps in participants who have been playing the game during the preceding hours. The induced hypnagogic hallucinations are stable over training days. They preferentially occur during sleep stage 1 and 2 and much less frequently during full-blown wakefulness or deep NREM sleep. Their nature is mainly visual and auditory, consistent with the task modalities, and occurrence rate is related to the best behavioral performance achieved over 3 days of practice.

The content of the hallucinations and their association to sleep onset allows some testable predictions about the organization of brain activity which they are associated with.

**Hypnagogic hallucinations can be induced during a nap following training**

Despite the strict rating by 3 independent judges, we recorded 48 Tetris-related reports at sleep onset out of 485 usable awakenings, i.e. a 10% rate of incorporation in the experimental group across three days. This contrasts with the 1% probability of reporting a Tetris-related hallucination in an independent group of volunteers who followed exactly the same procedures except for the practice of Tetris (1 report out of 107 during one experimental day) and the 3% probability when subjects anticipated on Tetris practice (3 reports out of 112 during one day). These data are strikingly similar to those reported following awakenings from nighttime sleep after Tetris practice (Stickgold et al, 2000): 12% of all reports were task-related in the experimental groups (novices 17%, experts 10%) and 1% in the control group.

It should be noted that a between-subjects design was preferred to a within-subjects protocol in order to avoid Tetris incorporation into hypnagogic mental activity due to anticipation inherent to the latter (Wamsley et al, 2010).

**Experience-induced hypnagogic hallucinations are associated with sleep stage 1 and 2**

Based on standard polygraphic recordings, our data indisputably show that experience-dependent hypnagogic hallucinations are closely related to sleep stage 1 and early stage 2 sleep, as is classically reported for hypnagogic hallucinations in general (Hori et al, 1994; Germain and Nielsen, 1997). This result is important because this transitory and unstable state of vigilance is associated with consistent changes in the regional organization of brain activity. During sleep onset, coherent spontaneous fluctuations in activity persist in the default-mode network (Horovitz et al, 2008). This network consists of a set of densely connected brain areas (medial frontal, posterior cingulate, precuneus, inferior parietal lobule; (Damoiseaux et al, 2006; Fox and Raichle, 2007), in which the activity increases when subjects are asked to rest (Gusnard and Raichle, 2001), a condition promoting self-referential thoughts (D'Argembeau et al, 2008), mind wandering (Mason et al, 2007) and the unfocused monitoring of the environment (Gilbert et al, 2007), akin to sleep-onset mentation. Accordingly, activity in the medial prefrontal cortex and precuneus increases at sleep onset, relative to full blown wakefulness (Olbrich et al, 2009). Beyond the recruitment of this anatomo-functional backbone, sleep onset is mainly characterized by increased activity in sensory cortices (visual, auditory, somatomotor; (Kjaer et al, 2002; Horovitz et al, 2008; Larson-Prior et al, 2009; Olbrich et al, 2009)), which potentially underlies hallucinatory sensory experience at sleep onset.

**Variety of experience-induced hypnagogic hallucinations**

Among all Tetris-related reports, 33% of the hallucinations corresponded to actual Tetris stimuli (16 out of 48). In keeping with their classical description (Foulkes and Vogel, 1965; Schacter, 1976; Mavromatis, 1987), these hallucinations were mostly visual and auditory. This was expected, given the visual and auditory nature of Tetris. The conspicuous absence of kinesthetic hallucinations contrasts with their high frequency after training to Alpine Racer (37% of imagery reports; (Wamsley et al, 2010)).

Again, this difference speaks for the tuning of hallucinatory content to the preceding waking experience.

Anticipation and experimental demand are not likely to explain the results. Indeed, significantly less Tetris-related reports were recorded in volunteers who knew they would practice Tetris after the nap, in contrast to (Wamsley et al, 2010) who reported an increased number of task-related reports on the baseline night. In addition, in the group who practiced Tetris before the nap, a large proportion of hallucinations could hardly be explained by experimental demand because they were not identified as Tetris elements by the volunteers themselves. Far from being mere reproductions of Tetris stimuli, these representations included associations with mnemonic components and transformations of actual Tetris elements into novel elements. Finally, similar proportions of Tetris-related reports were previously observed in amnesic patients (8%; (Stickgold et al, 2000)).

A substantial proportion of Tetris-related reports included mnemonic components: similar musical pieces heard in a different context, other board games, familiar objects spatially arranged as in Tetris. This finding suggests that Tetris-related memory traces interact with older memories and induce their spontaneous retrieval at sleep onset. Being preserved in amnesic patients (Stickgold et al, 2000), these representations potentially emerge from neocortical areas, mainly unimodal associative areas of the ventral (object identification) and dorsal visual streams (spatial arrangement, movements), unimodal auditory cortices or multimodal sensory cortices (Kjaer et al, 2002; Horovitz et al, 2008; Larson-Prior et al, 2009; Olbrich et al, 2009). The absence of affective content in Tetris-related hypnagogic hallucination speaks for the lack of recruitment of emotion-processing structures such as the amygdala and the reward system.

The mental images occurred without any reference to time or place and appeared, rather, to be extracted from the actual experience. This lack of temporal and spatial associations can be explained by the absence of hippocampal involvement in image construction, as

demonstrated in amnesic patients having the same Tetris-related hypnagogic imagery without remembering having played the game (Stickgold et al, 2000).

**Experience-induced hypnagogic hallucinations and learning**

Although obviously related to recent experience, the present data do not provide strong evidence that experience-dependent sleep-onset hallucinations are quantitatively associated with critical steps in memory processing. We could not confirm the correlation between initial performance and sleep-onset task-related imagery reported by others (Stickgold et al, 2000; Wamsley et al, 2010). We found that improvement in performance does not correlate with the frequency of imagery (Emberger, 2001) but, by contrast, that the rate of sleep-onset reports correlates with the maximal individual Tetris performance. However, the latter parameter does not selectively probe memory processes as it also heavily depends on other cognitive functions as alertness, focused attention and motivation during practice.

**Multiple awakenings did not affect the mental content**

It might be argued that repeated awakenings could produce an artificially high rate of Tetris-related hallucinations because multiple awakenings might change the volunteers' expectation about the experiment. This is not consistent with the data: thematic consistency in Tetris-related reports (either across days or over repeated awakenings within one day) appeared in a minority of reports only. They never occurred consecutively and were always interspersed among thematically unrelated reports. Therefore, although it remains possible that multiple awakenings affect the incorporation of Tetris elements, mental content did not seem to be systematically biased by prior Tetris-reports.

## 3.5. Conclusion and perspectives

Hypnagogic hallucinations, induced during daytime naps by prior practice of Tetris, occur predominantly at the transition between wakefulness and sleep, especially in

stage 1 and early stage 2 sleep. They mainly consist of visual and auditory hallucinations, consistent with the modalities of the task, often incorporating mnemonic components. These features predict that hypnagogic hallucinations may be associated with the state-dependent recruitment of mesial frontal and parietal areas and other components of the default mode network as well as with a persistent activity in neocortical unimodal or multimodal sensory areas previously recruited during prior wakefulness and in which recent experience can interact with previously encoded memories.

However, in the view of studying the cerebral correlates of memory consolidation using an objective method such as fMRI, hypnagogic hallucinations during daytime naps are not an optimal study design because only 10% of the reports consisted of task-related content, reported only by 13 out of the 16 volunteers. Therefore, we preferred to change our protocol to spontaneous brain activity during resting state wakefulness instead of sleep onset, which is described in the next research chapter of this thesis.

# 4. RESEARCH STUDY 2: RESTING STATE

This chapter is based on:

- Schrouff* J, *Kussé* C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding semi-constrained brain activity from FMRI using support vector machines and gaussian processes. PLoS One 7(4): e35860.
- Schrouff J, *Kussé C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding spontaneous brain activity from fMRI using gaussian processes: tracking brain reactivation. In: PRNI, London, doi 10.1109/PRNI.2012.19.
- Schrouff* J, *Kussé* C*, Wehenkel L, Luxen A, Maquet P, Phillips C (Submitted) Temporally structured memory replay during resting wakefulness in humans.
- *Kussé C*, Schrouff J, Phillips C, Maquet P (In progress) Dynamic causal modeling reveals temporally structured memory replay during resting wakefulness in humans.

Significance

Memory consolidation is thought to depend on the reactivation of patterns of brain activity that characterize recent experience. Although reactivation has been identified and well-described in the animal hippocampus, the persistence of cortical activity remains to be described in humans using non-invasive neuroimaging methods. Using multivoxel pattern analysis of fMRI data, we found that patterns of task-related brain activity in the ventral visual stream persist into immediate rest periods and that this persistence seems to be related to memory performance, suggesting that postlearning persistent activity patterns may contribute to memory consolidation. However, other analyzing techniques could not confirm these findings.

## 4.1. Objectives

The aim of this study is to characterize directly the neural correlates of memory consolidation during resting state wakefulness in healthy human volunteers, by examining the spontaneous processing of a visuospatial learning task with fMRI.

Memory consolidation is an unconscious process during which initially labile encoded memory traces are converted into more stable, long lasting memories which can later be recalled consciously (Squire et al, 1984). Although most researchers agree on the exposed framework for treatment of memory traces, many details of the initial stages of memory maintenance are still unknown (Miller, 2012).

First, we had to test whether or not we could detect memory traces in fMRI resting state subjects. It has been suggested that spontaneous repetitions of brain activity patterns, predominantly when the cortex is offline, could play a role in consolidating recently formed memory traces. Although animal and human studies support the theory of memory consolidation and give hints on its temporal aspect, they do not allow a non-invasive and direct characterization of memory traces during resting state wakefulness in humans.

Second, most studies examining memory processing in humans rely on memory retrieval (Polyn et al, 2005; Chadwick et al, 2010; Kuhl et al, 2011) or on the encoding phase (Kuhl et al, 2012b). Moreover, some studies are not immune to confounds such as concurrent practice or rehearsal of the learned material (Kuhl et al, 2013; Jafarpour et al, 2014). An experimental protocol allowing the direct characterization of memory consolidation without the confounding effect of memory retrieval needs to be established.

Third, some studies did not control for order effects. Therefore, it remains to be experimentally confirmed in different groups of volunteers that anticipation on task learning does not induce any modulation of brain activity.

Fourth, the temporal order of the reactivations remains unclear. A reactivation of temporally sequenced information has been reported, suggesting that the structure of the learning material, referred to as the phase information, has to be maintained during consolidation. The conclusions for individual neurons need to be verified for large neuronal populations, in particular for the phase information: do firing sequences of large neuronal populations mimic the discharges of individual neurons, which follow the sequence imposed by previous waking activity? Moreover, it remains unclear whether this reactivation occurs in the same or the reversed order as during the task. Moreover, it has to be confirmed if the reactivation of mnemonic cortical traces decreases over time and whether they are compressed in time.

Fifth and finally, it remains to be experimentally confirmed if the strength of the reactivations is linked to behavioral performance.

We address these questions using fMRI data of healthy human volunteers in a randomized within-subject cross-over experimental design. Volunteers were scanned during learning of a visuospatial task and pre- and post-task wakeful resting state periods. The same volunteers were also examined during a control task (an auditory oddball) with pre- and post-control resting states, the order of both tasks being randomized across participants. In order to unravel as much information as possible and obtain a complete overview of the ongoing brain processes, we resorted to four different state-of-the-art techniques:

- **Dynamic Causal Modeling** (DCM) (Friston et al, 2003) is a modeling approach that allows the analysis of effective connectivity patterns between distinct regions of interest (ROIs) within the cortical network (Friston et al, 2003). The advantage of DCM is that the measure of cortical connectivity is directional, allowing us to investigate the temporal aspect of activity in the three category-specific regions. Connectivity is important to examine because the functional role of any component of the brain, e.g. cortical area, sub-area, neuronal population or neuron, is defined largely by its

connections (Friston and Price, 2001). While DCM has been shown powerful to study the differences between consciousness states such as anesthesia (Moran et al, 2011), coma (Boly et al, 2011), sleep (Jahnke et al, 2012) and examining category-specific effects (Mechelli et al, 2003), it has not yet been applied to investigate memory processing.

- **Cross-correlations and explained variance** assess how much of the variance of the BOLD signal after learning can be explained by the signal during the task, after taking into account the baseline activity already present before the task. Such analyses have been applied to examine task-related replay of brain activity between simultaneously recorded neuron pairs in rodents, which found an explained variance of 5% during slow wave sleep before a specific behavior that augmented to 10% à 15% during sleep afterwards in rat hippocampus (Kudrimoti et al, 1999), ~10% in rat ventral striatum (Pennartz et al, 2004), 11% in rat prefrontal cortex, and 5 à 11% in monkey cortex (Hoffman and McNaughton, 2002). The reasoning is that cells that fire together when the animal is learning a task, show an increased tendency to fire together during subsequent sleep, consistent with an underlying associative synaptic modification.

- **Spatial networks identification**, based on Independent Component Analysis (ICA), allow automatic identification of the functional brain networks and measure the functional interactions within and between the networks by computing correlation coefficients between all possible pairs of ROIs. An advantage of this technique is that integration measures can be computed at the level of the whole brain, network and ROI. It has been applied for example to examine subcortical resting state networks (Malherbe C et al, 2010).

- **MultiVariate Pattern Analysis** (MVPA) is an innovative machine learning application which leads to the decoding of spontaneous brain activity: it is based on a classifier which is trained to link specific patterns of brain activity to a particular cognitive, behavioral, perceptual or medical state (Haynes and Rees, 2006;

Norman et al, 2006) (Figure 8). Neither the spatial nor temporal dimensions of the data are reduced, which is an important advantage when searching for spatially distributed and transient events of memory replay. The temporal aspect can be investigated as well. Application of these methods in the context of memory processing made it possible to predict the actually presented stimulus (Haynes and Rees, 2005a, 2005b) and the relation of encoding strength to memory performance (Kuhl et al, 2012b), but also, in the absence of any stimulus, decoding the mental content: the category of a mentally retrieved object (Polyn et al, 2005; Hassabis et al, 2009; Schrouff* et al, 2012), the category of perceived objects (Spiridon and Kanwisher, 2002; Cox and Savoy, 2003; Shinkareva et al, 2008), orientation of patterns (Kamitani and Tong, 2005; Haynes and Rees, 2005a), mental states related to memory retrieval (Polyn et al, 2005; Chadwick et al, 2010; Kuhl et al, 2013) or even hidden intentions (Haynes et al, 2007).

## 4.2. Material & methods

### 4.2.1. Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Regarding safety concerns, patients were informed about the large magnetic field and safety precautions of the MRI scan. They had to complete a written metal check questionnaire, which was double checked orally. Moreover, the absence of any metal was triple checked by a portable metal scan. All participants were fully informed about the protocol, gave their written informed consent and were paid for their participation.

### 4.2.2. Population

All included volunteers were young (19-29), non-smoking, right-handed healthy students with normal or corrected-to-normal vision. They were non-smoking, moderate caffeine and alcohol consumers, and none was on medication (except for oral contraceptives for women). None had been working night shifts or travelled across more than one time zone during the last 2 months. The absence of medical,

traumatic, psychiatric or sleep disorders was established in a semi-structured interview.

The volunteers were screened with standardized questionnaires for excessive daytime sleepiness (Epworth Sleepiness Scale score ≤ 10; (Johns, 1991)), sleep quality (Pittsburgh Sleep Quality Index Questionnaire score ≤ 8; (Buysse et al, 1989)), chronotype (Horne and Ostberg morningness-eveningness questionnaire score >30 and <70 (Horne and Ostberg, 1976)), anxiety (Beck Anxiety Inventory score ≤ 8; (Beck et al, 1988)), depression (Beck Depression Inventory II score ≤ 13; (Steer et al, 1997)) and laterality (right-handed according to the Edinburgh Inventory; (Oldfield, 1971)).

The amount and content of their dreams was examined with the London Sleep and Dreaminess Questionnaire (not yet validated), Waterloo Sleep Experiences Scale (Cheyne et al, 1999), dream diary, and the amount and content of their daydreams with the Imaginal Process Inventory (http://www.neuroinfo.org/w/public/images/5/55/Ipi.pdf).

During the 7 days preceding the experiment, volunteers followed a regular sleep schedule, verified by a sleep diary and wrist actigraphy (Actiwatch, Cambridge Technology, UK). Subjects were instructed to eat normally but to abstain from stimulants (such as coffee, tea, coca cola, red bull, etc.) and cigarettes. All questionnaires were presented in the volunteer's native language, i.e. French, Dutch or English.

### 4.2.3. Experimental design

All volunteers underwent two main conditions (Figure 22): a control condition and a memory condition, their order being randomized across participants to avoid time effects. Half of the volunteers (6 of which 3 women) first underwent the memory condition while the other half (5 of which 2 women) first underwent the control condition.

| | | | | | | |
|---|---|---|---|---|---|---|
| memory condition | *fMRI* localizer 5′ | *fMRI* **rest 1 10′** | **exploration 24′ encoding** | **rest 2 10′** | **imagery ± 25′ retrieval** | memory test ± 20′ retrieval |
| control condition | | rest 1 10′ | oddball 24′ | rest 2 10′ | | |

Figure 22. Experimental protocol. In the fMRI scan, subjects underwent a visual encoding task, flanked by two rest sessions and followed by a retrieval session (upper part in black text), as well as an auditory control task flanked by two rest sessions (lower part in gray text). A functional localizer preceded the memory condition to avoid novelty effects. Performance was checked after scanning in a memory test.

**Memory condition**

The core of the experiment consisted of four fMRI sessions: a visuospatial task (encoding) flanked by two rest sessions and followed by a mental imagery session (retrieval) (Figure 22, bold text in the upper part).

Preceding these four sessions was a functional localizer session (Figure 23) during which the images involved in the learning task were presented at the center of the screen in a random order, in an event-related design. They represented neutral photographs in color on a white background. The purpose of this session was both to identify brain areas responding to the image categories and to eschew novelty effects during subsequent sessions, ensuring an optimal stability of the BOLD response during task learning.

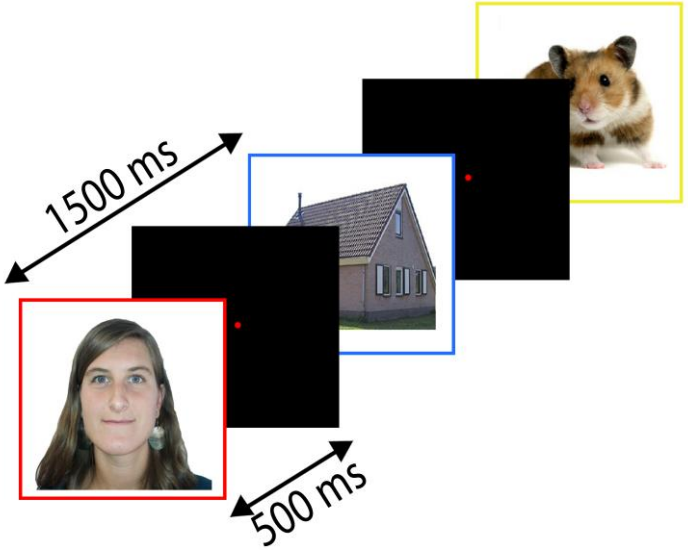


Figure 23. Functional localizer. Images of faces, buildings and animals were presented to the subject for 500ms with an inter-stimulus interval of 1500ms. In total, 81 different images were used.

During the memory encoding task, also referred to as exploration, the same images of faces, buildings and animals were displayed one at a time, each image being assigned a specific location on the screen. These categories of stimuli have been selected because they are dealt with in category-specific regions in the ventral visual stream (Downing et al, 2006). The order of presentation followed a predefined sequence of screen positions in such a way that volunteers had the impression of following a path throughout a bidimensional trajectory or maze covering the entire screen (i.e. approximately 9 degrees of the volunteer's visual field) (Figure 24, upper part).

Each picture was displayed at a specific screen position and pictures were organized in blocks of 9 contiguous images of the same category (faces, buildings, or animals). Blocks were spatially arranged such that a counterclockwise navigation through the maze implied a fixed and repeated succession of blocks of faces, buildings and then animals. Between blocks, a fixation cross was displayed for 15-18 seconds. The size of the stimuli was ~0.8 visual degrees. To ensure optimal encoding, the whole path of 81 images, each shown for 3 seconds, was repeated five times. Participants were instructed to memorize the position and content of each picture as well as the order of appearance. Importantly, the complete structure and overview of the trajectory were never available to them.

The retrieval session inside the fMRI scan (Figure 24, lower part) consisted of a mental imagery task: volunteers were presented two images, representing the start and end positions of a path that the volunteers would have to follow mentally, one image at a time. A total of 54 trials were presented. During each trial, two images of each 3.3 visual degrees were simultaneously displayed on the center of the screen for 8s. The mental trajectories included 3 to 6 images (average 4.5) within a single image category. For each image that they could conjure up during this mental travel, volunteers had to signal by a key press whether it was a face, a building or an animal they had in mind (one finger and key per category). However, participants also had the possibility to skip a trial if they could not remember any part of it. The expected number of images of each type was

perfectly balanced between categories. Event duration was not fixed and depended entirely on the speed at which each subject recalled the requested images, resulting in event durations varying between 200 ms and 4000 ms with most events during less than 2000 ms.

Ten-minute rest sessions, during which participants stayed immobile, eyes closed, were scheduled immediately before and after encoding. Importantly, participants were instructed only to relax, let their mind wander and stay awake. These rest sessions were our state of interest: we reasoned that changes in spontaneous brain activity between the two rest sessions should reflect changes induced by learning, i.e. the neural correlates of recent memories.

**Performance**

At the end of the experiment, a memory retrieval test was performed outside the scanner, in order to behaviorally assess the accuracy of the spatial and content knowledge acquired by the volunteers. They were presented with the 81 previously seen pictures from the maze and 48 novel images of the same categories in random order. For each trial, an image was displayed on the screen at a specific location. Participants first had to specify whether this image was part of the maze and, if they believed it was, if it was displayed at its correct location. To this end, a two-dimensional grid was displayed both during the learning session and this task. The behavioral performance was based on *discrimination ability d'* of image content (Green and Swets, 1966). Note that this behavioral recognition test relies on different memory systems than the retrieval session inside the fMRI: the latter involves binding of multiple items into a sequence of events.

*Sensitivity index or discrimination index d'* is derived from signal detection theory. Higher values of d' indicate better discrimination ability, i.e. a better performance.

$$d' = \frac{z\,(\text{probability of hits})}{z\,(\text{probability of false alarms})}$$

Participants were also asked at the end of the scanning session whether they had mentally rehearsed the learning task during the following rest sessions. If so, they had to estimate the number of mentally rehearsed pictures during

this session and whether rehearsal was intentionally or occurred spontaneously.


Figure 24. Experimental setup. During encoding, each image occurred at a specific position on the screen. A synoptic view of the 2D maze is represented [red areas, images of faces (F); blue areas, buildings (B); yellow areas, animals (A)]. During the retrieval session, participants have to mentally perform the trajectory linking start and end points displayed on the screen, conjuring up images comprised in the trajectory and pressing a key every time he retrieves the required image.

**Control condition**

To account for non-specific (order and fatigue) effects, the same participants were examined on another condition. The control condition allows us to ensure that eventual activity changes between the pre-task and post-task rest sessions in

the experimental condition, are indeed due to the experimental task and not to a mere time or order effect.

The control group was examined following the exact same protocol, except that the visuospatial memory task was replaced by an auditory discrimination task based on an oddball paradigm (Figure 22, gray text in the lower part). This task does not imply any long-term memory component or any visual stimulus and does not recruit the regions in the ventral visual stream. The auditory oddball paradigm had exactly the same duration as the memory session, namely 24minutes. Volunteers had to listen to a series of beeps and count the odd tones. Eight times more beeps of 1400Hz occurred than the odd ones of 700Hz. Each sound lasted for 250ms and was followed by a blank of 1750ms (Figure 25). Sound volume was adjusted just before the task by each volunteer, so that each frequency could be heard clearly above the noise of the working fMRI. Volunteers were instructed to count the odd tones and report this to the experimenters at the end of the task.

In consequence, the critical analyses compared 4 rest sessions (before/after task, memory/oddball conditions).

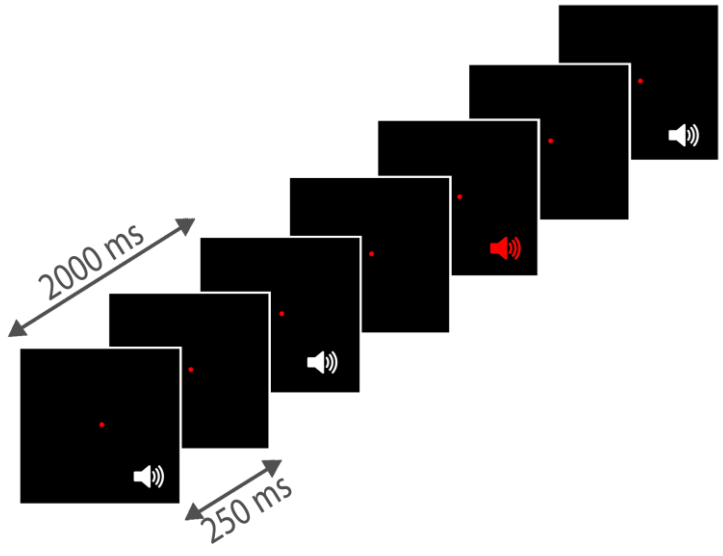


Figure 25. Auditory oddball. The frequent sounds of 1400Hz occurred eight times more than the odd sounds of 700Hz. Each beep lasted 250ms with an inter-stimulus interval of 2000ms. In total, 92 odd sounds were used. A red fixation cross was displayed continuously on a black background.

*fMRI* is a non-invasive way to measure regional changes in cerebral metabolism, cerebral blood flow and blood volume in response to neural activity, using a method based on the blood oxygenation level dependent or BOLD signal (Ogawa et al, 1990).

In *T2 or T2* weighted imaging*, cerebral white matter (containing fat) appears darker than gray matter; cerebrospinal fluid and blood (containing water) appear bright.

In *T1 weighted imaging,* tissues efficient in exchanging energy, such as fat, cerebral white matter and bone, have high signal intensity. Cerebrospinal fluid, water and blood, appear dark. If a high resolution is needed, whole brain coverage takes much longer than the EPI sequences, in the order of minutes instead of seconds. For structural images, slices are usually thinner than functional images, for example 1 mm.

## 4.2.4. fMRI data acquisition

**Functional time series**

All *fMRI* time series were acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. Multislice *T2*-weighted* functional images were acquired with a gradient-echo echo-planar imaging sequence (EPI) using axial slice orientation and covering the whole brain: 34 slices, FoV 192x192mm², voxel size 3x3x3mm³, 25% interslice gap, matrix size 64x64x34, TR per slice 60ms, TR per volume 2040ms, TE 30ms, TA 1980ms, FA 90°, 220 μs echo spacing, bandwidth 3551 Hz/Px, slices acquired in ascending order with the 17$^{th}$ slice as reference.

**Field mapping sequence**

For unwarping purposes, static field inhomogeneities were measured immediately after the EPI time series in order to be in the same conditions regarding shimming and head position, using a field mapping sequence with the same brain coverage and slice orientation. This gradient-recalled sequence acquired two complex images with different echo times (TE 4.92 and 7.38ms respectively, TR 367ms, FoV 230x230mm², 64x64 matrix, 34 transverse slices, 3mm thickness, 25% interslice gap, 3.6x3.6x3mm³ voxel size, FA 90°, bandwidth 260 Hz/Px) and was used to generate field maps for distortion correction of the functional images.

**Structural image**

Finally, for anatomical reference, a high-resolution *T1-weighted* image was acquired for each subject using a 3D MDEFT sequence (Modified Driven Equilibrium Fourier Transform) with 1 mm isotropic spatial resolution. FoV was slightly increased (93.8%) in the phase-encoding direction to avoid aliasing of the nose in the visual cortex (176 sagittal slices of 1 mm thickness, 3D phase-encoded, TR 7.92ms, TE 2.4 ms, TI 910 ms, FA 15°, FoV 256x240x176mm³, BW 195Hz/Px, TA 12:51). This sequence is optimized (Deichmann et al, 2004) in order to get a higher contrast-to-

noise ratio between white matter and gray matter with better homogeneity through the whole brain (compensation for B1 inhomogeneities).

### 4.2.5. Data analysis

Our complex dataset presents challenges that are difficult to solve using standard neuroimaging analyzing techniques such as univariate models. Therefore, we apply several state-of-the-art techniques in order to obtain as much information as possible about the distributed cortical network for perception of faces, buildings and animals in resting state: dynamic causal modeling, cross-correlations and explained variance, spatial networks identification, and multivoxel pattern analysis.

#### 4.2.5.1. Preprocessing

Before data analysis, the functional time series had to undergo several preprocessing steps (Figure 26, left panels).

First, the three initial volumes of each EPI time series were discarded to avoid T1 saturation effects.

In the next step, the images were corrected for differences in slice acquisition timing: slices were acquired in ascending order, and corrected to the middle slice.

Spatial distortions or deformations caused by static field inhomogeneities were now estimated in a voxel displacement map using the Fieldmap toolbox (Hutton et al, 2002). They were simultaneously realigned and unwarped (Andersson et al, 2001) to account for the subject movements in the scanner and for the interaction between these movements and the spatial deformations.

Then, all functional time-series were coregistered to the subject's own structural image.

In a further preprocessing step, the images were segmented in white matter, gray matter and cerebrospinal fluid, and functional images and high resolution structural images were normalized to a standard space in order to allow

The *MNI template* is an EPI template of the Montreal Neurological Institute, an average image of 305 anatomical images.

between-subject comparisons. We used the *MNI template* (Collins, 1994).

Finally, the images were smoothed using a Gaussian function with an 4 mm full-width at half-maximum kernel in order to reduce slightly the high frequency spatial noise in the images, while keeping a good spatial accuracy (Cukur et al, 2013), and hence improve the signal-to-noise ratio. Residual interindividual differences are minimized (Friston, 2004), making them suitable for statistical analyses.

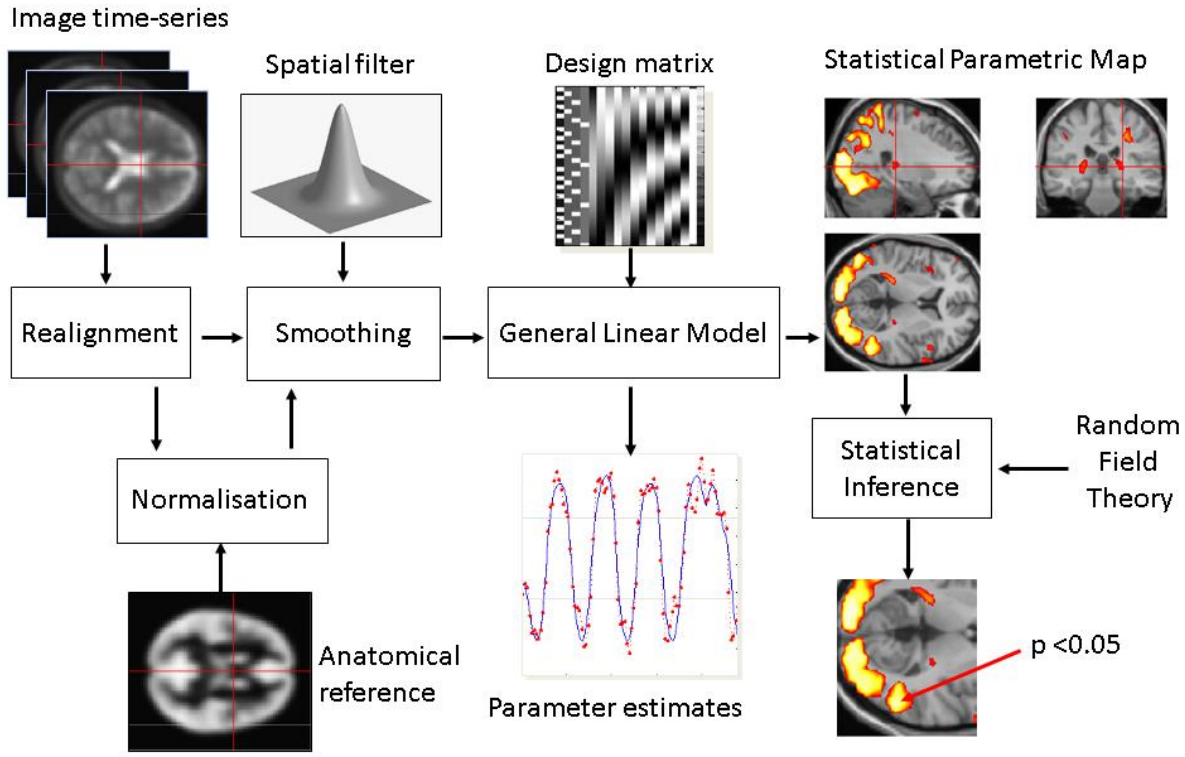


Figure 26. Schematic representation of the preprocessing and conventional statistical analysis of fMRI data using SPM.

#### 4.2.5.2. Univariate analysis

We applied a GLM, a multiple regression model which considers the voxels in a mass univariate way (Kiebel and Holmes, 2004), to the maze learning session in order to identify the anatomical locations of the ROIs of the 3 stimulus types, based on stimulus onsets (Figure 26, middle and right panels). In the model specification, the time series were high-pass filtered to eliminate low-frequency components (cutoff: 1/128Hz) and adjusted for estimated movements using multiple regressors (the realignment parameters), effects that would not be convolved with the hemodynamic response and hence may confound the data.

A *T-test* is any statistical test in which the test statistic follows a T distribution if the null hypothesis is supported. A T-test is either positive or negative.
An *F-test* is any statistical test in which the test statistic has an F distribution under the null hypothesis. An F-test can be viewed as testing for the additional variance explained by a larger model.

**Exploration session**

We first applied an *F-test* to determine the main activation of the task irrespective of the category of images, i.e. all the voxels whose activity was statistically significantly correlated with any of the three conditions. The statistical map was thresholded at p<.001 voxel level (not corrected for multiple comparisons) and the ensuing mask was further used for time series extraction.

In the *first level FFX* (fixed effects analysis), it is assumed that all subjects correspond to the same model. Only within-subject variance is used in this kind of test. The purpose of the FFX is to find only those areas that are activated on the average across volunteers.
In the *second level RFX* (random effects analysis), it is assumed that different subjects might correspond to different models. RFX considers both within- and between-subject variance. The purpose of the RFX is hence to find areas that are activated in the same way in all volunteers.

The first level within-subject *FFX* each category of stimuli is compared to the average of the other two, producing 3 contrast images per subject. At the second level between-subject *RFX*, 3 separate *T-tests* are used to find the main effect of each category, i.e. those voxels that are more active when all volunteers viewed one category than the mean activity when seeing the two other categories. The main effect of each category was further used for ROI selection.

The anatomical locations of the ROIs were defined by superimposing the RFX statistical maps on the high resolution structural image. We used the mean of our dataset instead of the MNI template in order to estimate more accurately the exact location of the ROIs. The center of the responses were defined as the global maximum of responsive voxels with a significance threshold set to p<0.001 (not corrected for family-wise errors, FWE).

**Rest sessions**

For the rest sessions, the extracted signal was adjusted for realignment parameters through a GLM.

#### 4.2.5.3. Stochastic DCM

In order to examine the effective connectivity and causal influences between the 3 category specific regions during resting state, we used *stochastic DCM*.

*Stochastic DCM* extracts patterns of effective connectivity from resting state brain activity. This parametric statistic approach examines how the endogenous activity of one region drives that of another region (Wertz et al, 2006; Daunizeau et al, 2009).

First, we determined the ROIs from the exploration session (see previous section): spheres containing 27 voxels were selected for each ROI in the right hemisphere. Then, we extracted the signal of these voxels during the rest sessions and summarized them into a single time series per region, per session and per subject, using a principal component decomposition (the 1st component is kept).

Second, we defined the model space (Figure 27). Because of the absence of any driving or modulatory input in the resting state sessions, a stochastic DCM was employed (Daunizeau et al, 2009). We applied DCM on the extracted time series of the rest sessions in two different approaches:

- For one approach, we explored every possible model, i.e. models containing all possible combinations of connections.

*Bayesian* probability measures a degree of belief in a hypothesis. For testing model evidence, i.e. finding the model or the family of similar models with the most likely connections and best explaining the measures responses, this means that Bayesian inference is relying on prior knowledge about the connectivity parameters.

- For the other approach, we explored also subsets of models, i.e. three families of models of interest (Figure 28). Our model selection was based upon two experimental evidences of memory consolidation: replay in the learned order (i.e. a first family with forward connections in the direction from FFA to PPA to AA, back to the FFA) or inverse order (i.e. a second family with backward connections from FFA to AA to PPA, back to the FFA). The third and last family contained the fully connected model, which could not be excluded because anatomical connections are not yet explored for this brain area.

Third, *Bayesian* model selection (random effects inference) was applied to select the (family of) model(s) with the best

evidence, i.e. best explaining the observed data (Friston and Penny, 2011).

Next, we examined the parameters of the models on connection strength (Friston and Penny, 2011), namely the intrinsic coupling between regions, changes in coupling due to external input, and direct influences of inputs on the regions. Correlations with the number of rehearsed images and d' were tested using the Spearman rank correlation coefficient.

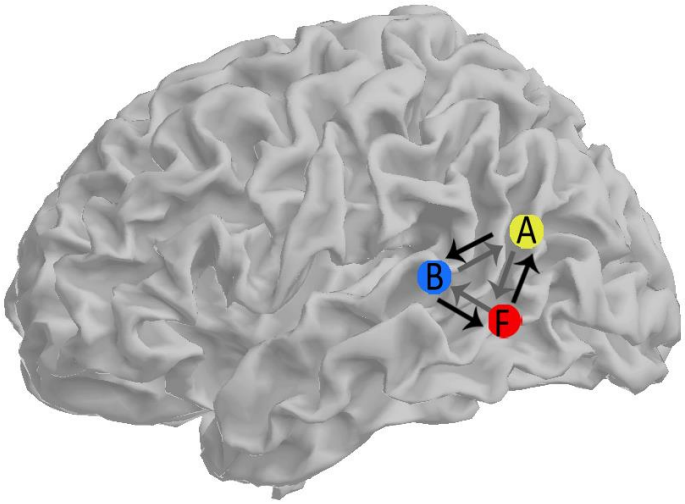


Figure 27. DCM models. Forward connections (F-B-A, gray arrows) and backward connections (A-B-F, black arrows) between FFA (red F), PPA (blue B) and animal area (yellow A).

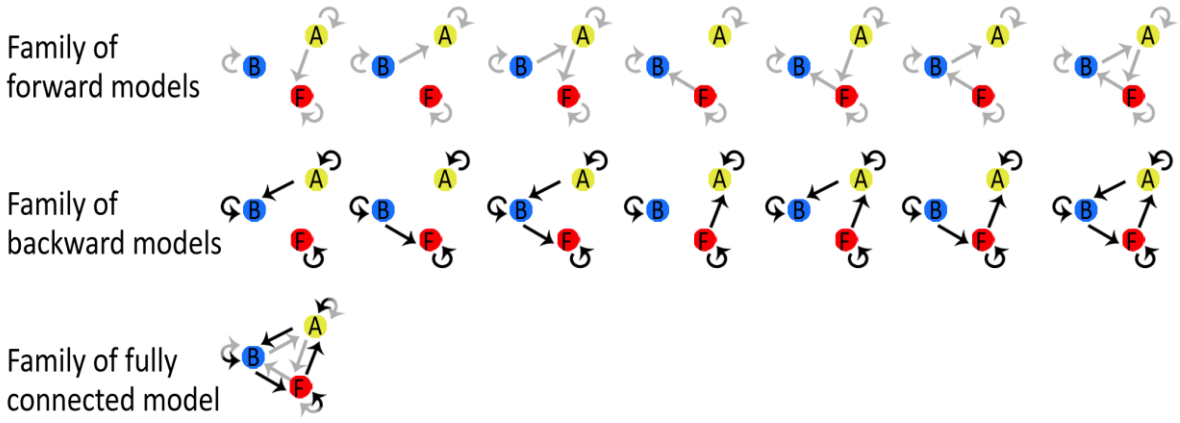


Figure 28. DCM model specification. The 14 DCM's used for Bayesian model comparison in the second approach. Upper part: family of models with only forward connections (gray arrows). Middle part: family of models with only backward connections (black arrows). Lower part: family with the fully connected model. Intrinsic connections are always present.

#### 4.2.5.4. Explained variance

To quantify the dynamics of memory trace reactivation during post-task rest, we computed how much of the variance of the BOLD signal during the post-task rest session could be explained statistically by their signal during the learning task, after taking into account the baseline activity already present in the pre-task resting session.

First, we selected 3 ROIs for each volunteer and for each category separately (faces, buildings and animals), similar as for DCM analysis, see 4.2.5.3.

Second, to continue the analysis with only one timecourse per ROI, per session and per subject, we employed a principal component analysis and used the first component. The signal was detrended in order to remove linear and nonlinear trends. Scaling was checked, enforcing a maximum change of 4%, in line with DCM processing. Next, the signal was filtered with a butterworth filter: a bandpass filter of order 4 with a high and low cutoff frequency of 0.008 TR and 0.16 TR, which corresponds to 0.0163 Hz and 0.3264 Hz respectively.

Third, we tested three different strategies for extracting data from the time series. For all strategies, the complete 10 minutes of resting state were used:

- For the first strategy, the complete timecourse of the exploration task and the rest sessions were extracted for the three ROIs.

- For the second strategy, only epochs of 8 scans at the transition from one stimulus to another were considered. The pauses between blocks were simply excluded from further analysis.

- For the third strategy, we flipped the transition epochs in time and compared them with the normal epochs.

An *explained variance* of 100% would mean that the activity during the task and post-task rest were identical.

Next, the *explained variance* (EV) of the correlation pattern during post-task rest, caused by the learning task, was

computed using the square of the partial correlation coefficient, as in (Kudrimoti et al, 1999):

$$EV = r^2_{task,\ post\ |\ pre}$$

where $r_{task,\ post\ |\ pre}$ reflects the effects of the learning task on the activity correlations in the post-task rest, after controlling for any pre-existing relationship that might have been present in the pre-task rest.

We tested the significance level of the differences in EV with the Mann Whitney U test. All p-values were Bonferroni corrected for multiple comparisons.

#### 4.2.5.5. Spatial networks identification

In order to study the functional interactions between the resting state networks in the brain at the group level, we used NEDICA (network detection using ICA) of NetBrainWork, which is a Matlab toolbox for processing resting state fMRI datasets using independent component analysis (ICA) ((Perlbarg et al, 2009), sites.google.com/site/netbrainwork).

First, images were registered into the MNI standardized space before performing a hierarchical clustering on the IC. A group T-map was associated with each category (Perlbarg et al, 2008b). Functional resting state networks, known from the literature (Damoiseaux et al, 2006), were selected from the T-map and used for subsequent analysis as the main networks of interests (NOIs, Figure 29).

Second, ROIs of 20 voxels were selected around the peaks of each group T-map, at least 4 cm apart. Since they were detected on the rest sessions, these nodes were not the activated areas during the learning task. We therefore manually added two networks with regions based on the GLM analysis of the task learning: one hippocampal network, and one maze network comprising the FFA, PPA and AA.

Third, *CORSICA* was employed to identify and remove components related to physiological noise (Perlbarg et al, 2007). The functional interactions within and between the

*Spatial networks* combine automatic identification of the functional large-scale brain networks at the group level, and ROI-based analyses to measure functional interactions within and between networks (Figure 29). This allows comparing the interaction at different brain scales between groups of subjects or different experimental conditions (Perlbarg and Marrelec, 2008a; Perlbarg et al, 2008b).

*CORSICA* (correction of structured noise using spatial independent component analysis) uses prior information on the spatial localization of the main physiological fluctuations in fMRI data. The technique includes 3 steps:
- spatial ICA decomposition
- selection of noise-related components using specific masks of interest comprising the ventricles, brainstem and basilar arteries
- removal of these noise components.

*Functional integration* is the analysis of effective connectivity: how did the experimental manipulation propagate through the network? (Marrelec et al, 2008).
*Functional specialization* or *segregation* on the other hand is the localization of brain activity: where in the brain did the experimental manipulation have effect?
*Partial correlation* measures the degree of association between two random variables, with the effect of a set of controlling random variables removed.

NOIs were quantified with hierarchical *integration* and *partial correlation*. In this study, integration was estimated 1000 times and presented as the mean and its standard deviation.

Fourth, since hierarchical integration provides a global measure of interaction, it is unable to quantify pairwise functional connectivity. To do so in a given network, we resorted to partial correlation (Marrelec et al, 2009; Smith et al, 2011) which was computed using the 1000 samples of the Bayesian numerical sampling scheme (Marrelec et al, 2009). The density of connections at a given threshold was computed as the number of ROI pairs for which partial correlation was above the threshold. A connectivity curve was obtained by computing the density of connections across a range of thresholds. Finally, the integrated difference in partial correlations (IDPC) was computed, which is independent from the threshold and quantitatively estimates the differences in connectivity between conditions.

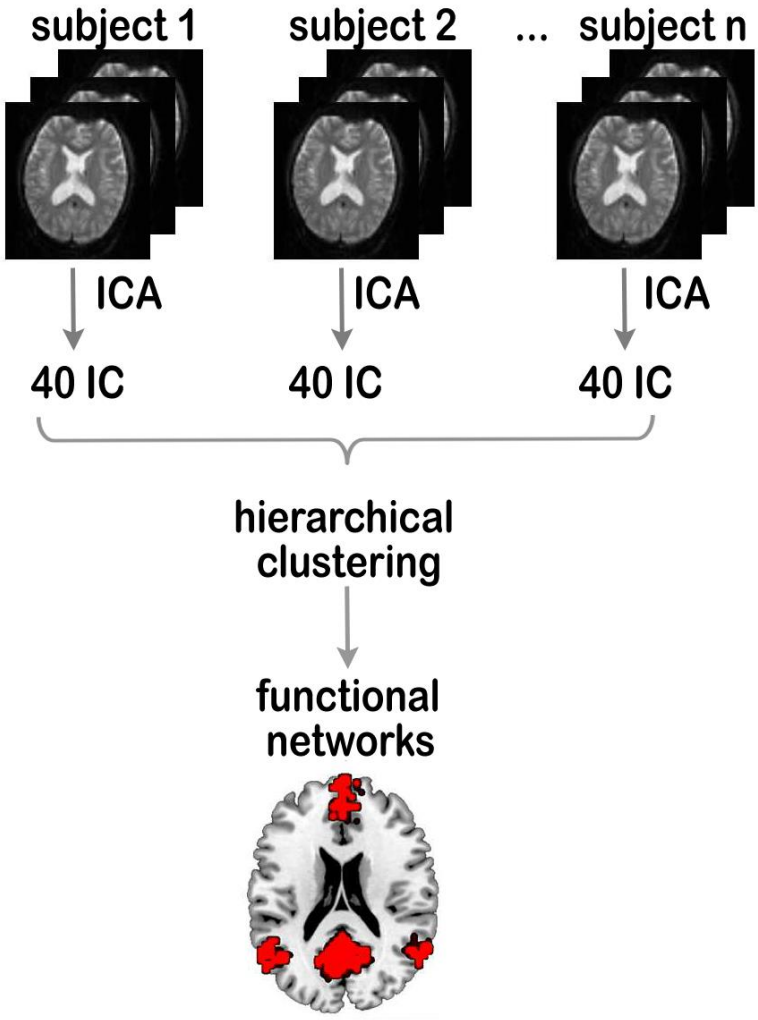


Figure 29. Computing integration and partial correlations at the group level. A spatial ICA was applied on each subject, leading to 40 IC (default value) which were then hierarchically clustered. IC corresponding to noise processes (such as cardiorespiratory artifacts) or not characteristic of any previously identified network were discarded. Group T-maps were then computed revealing functional networks at the group level. From these maps, ROIs were automatically selected and used for computating integration and partial correlations via a 1000 samples Bayesian numerical sampling scheme of the posterior distribution. Figure and caption adapted from (Schrouff, 2013).

#### 4.2.5.6. Multivariate pattern analysis

We examined the patterns of task-related brain activity during resting state with machine learning based models using multivariate classifying techniques that reduced neither the spatial nor the temporal aspect. Therefore, this technique allowed us to test different features of offline memory processing, such as the spatial distribution but also the temporal evolution and phase information.

*MVPA* decoding techniques are based on distributions or patterns of responsive voxels. MVPA methods require at least two separate datasets:
- In the training phase, the classifying model is built and trained on a large dataset. All scans of the time series receive a label to which category they belong (F,B, or A in our experiment) and the model hence learns, i.e. builds a mathematical algorithm, to discriminate between the patterns of activity of the different categories in order to classify them in the correct category, helped by the labels.
- In the test phase, this model is applied to a test set, which does not contain any label. The model hence has to predict to which category the test set corresponds, based solely on the pattern of brain activity.

First, in order to test which machine learning-based model would be optimal for our experiment, two classifiers (*SVM* and *GP*) using different univariate and multivariate feature selection steps (GLM and/or SVM) were applied on the task learning (encoding) and mental imagery (retrieval) sessions. Note that this part of the experiment was a preparatory step, necessary for the next part which is the main goal of this thesis, and will not be further described here. For supplementary information about the methodology and the results, we refer the reader to the design optimization paper (Schrouff* et al, 2012).

Then, the classifier with the highest accuracy (GP, because this technique tended to be more robust than SVM to model unbalanced data sets) was trained on the mental imagery session and applied to each rest session. This part of the experiment is the goal of this thesis and will be described in detail in this chapter, namely: what is the signal of interest (signal extraction), where is it located (feature selection) and how are patterns defined (classification procedure). The retrieval session was chosen as training set because 1) cognitive processes are less controlled than during encoding; 2) it has an increased variance because the duration of the session was self-paced; and 3) it implied an activation of recent memories in the absence of visual input, i.e. the condition closest to potential spontaneous replay during resting sessions.

**Signal extraction**

After pre-processing, the signal was extracted and adjusted. For the sessions considered for further modeling (i.e. the retrieval session and the 4 rest sessions for each subject), the whole time series of all voxels were used (i.e. without consideration of experimental design). The data matrix was then adjusted for movement effects (estimated by realignment parameters) and low frequency drifts (cutoff: 1/128 Hz) using a GLM (Friston et al, 2007).

For the retrieval session, the signal corresponding to stimulus onsets was then extracted, considering a hemodynamic response function (HRF) delay of 6 seconds. To avoid decoding the signal linked to motor activity, the

scans selected for further classification were the ones preceding the key presses (after correction for HRF delay). The signal was finally averaged over specific time-windows to increase the signal-to-noise ratio (Kamitani and Tong, 2005; Mourao-Miranda et al, 2006). For the retrieval session, this average was performed over the interval between two key presses, with a maximum of 2 scans (i.e. 4080 ms) to avoid the inclusion of episodes of task-unrelated thoughts. For rest sessions, each scan was considered as a sample and the adjusted data matrix directly entered the test phase of the classification without any further processing.

*SVM (support vector machine)* uses a cost function for defining a decision boundary in order to assign a label to each datapoint (Burges, 1998). SVM is a sparse method because only a few support vectors (i.e. the nearest datapoints to the hyperplane) are used to define the separating hyperplane.

**Feature selection**

In this work we considered a univariate filter based on the results of a GLM analysis followed by a multivariate wrapper, *selecting features* according to the accuracy of SVM classifiers (Guyon and Elisseeff, 2003). For a detailed description of this procedure, we refer the reader to the paper of (Schrouff* et al, 2012) and Figure 30.

*GP (Gaussian processes)* is based on the concept that all datapoints have normal (Gaussian) distributions. As opposed to SVM, the number of support vectors in each category in GP is not related to the number of data points per category (Rasmussen and Williams, 2006), and for each input datapoint, there is a classifying output and an associated probability, which might carry important information. An advantage is that GP is more suitable for classifying imbalanced categories. A disadvantage is the risk of overfitting, i.e. when the model begins to fit noise.

The univariate filter determined, from a GLM analysis, the subset of active voxels (i.e. whose activity was statistically significantly correlated with the three conditions) (Mitchell et al, 2004). From the resulting F-maps, the 1000 voxels with the highest F-values were selected (Shinkareva et al, 2008).

The multivariate feature selection was based on binary SVM classifiers using linear kernels to rank the voxels according to their discriminating power, which was computed from their specific weights (Mitchell et al, 2004). In order to differentiate between the 3 categories of stimuli (faces, buildings and animals), we used 3 binary classifiers. The voxels with the largest absolute weights were selected for further modeling. The number of selected voxels systematically varied from 5 (per condition and binary comparison) to 130 at most, by increments of 25.

At each iteration, the sum of the accuracy of the three binary models on a left-out block was taken as a global accuracy measure (Table 6), the selected subset of features corresponding to the maximum of global accuracy. Features were thus added recursively following a recursive feature

*Feature selection* is the selection of a subset of voxels containing as much information as the whole set. Advantages are reduced computational requirements and increased signal-to-noise ratio, thereby improving overall classifier performance (Guyon and Elisseeff, 2003).

addition (RFA) procedure, which can be assimilated to a forward wrapper feature selection, with a cost function based on the global accuracy as objective.

The feature selection steps were performed on the training set only, to ensure unbiased estimations of the accuracy. To estimate model accuracy on the retrieval session, a nested cross-validation scheme was therefore needed. The model was then built using all data from the retrieval session and applied to the rest sessions. In this latter case, feature selection was obtained through a simple cross-validation (similar to the nested cross-validation of the former case) as no testing (on a left out sample) was performed. For more details on the feature selection and modeling strategy, please see (Schrouff* et al, 2012).

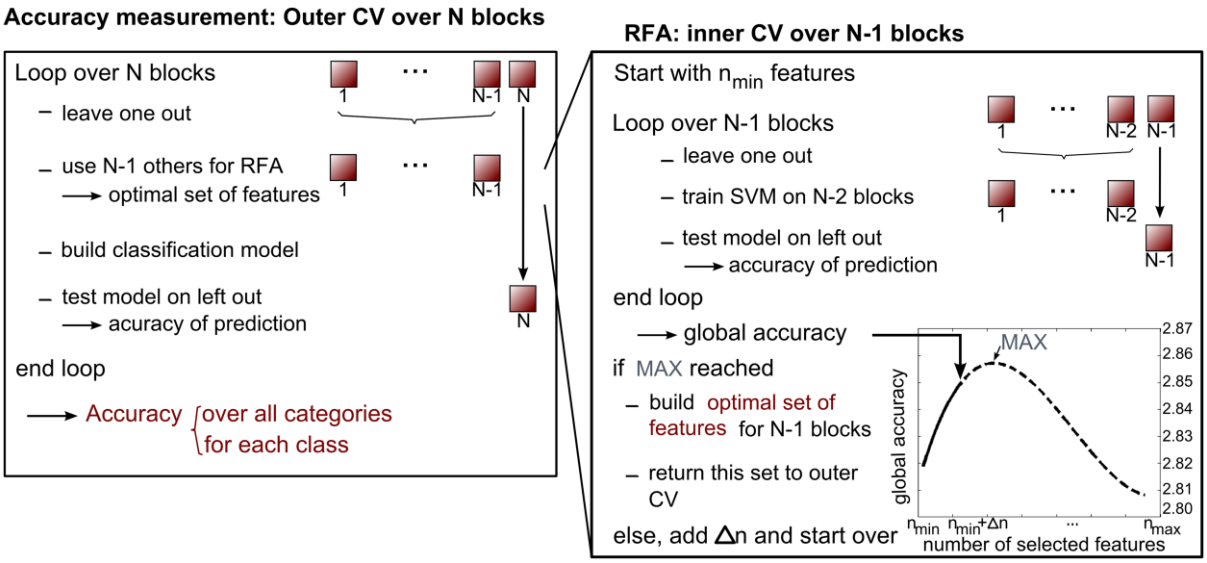


Figure 30. Recursive Feature Addition (RFA) process and Cross-Validations (CV). The accuracy measure is presented in the left box: from the outer CV, one block (containing m events) is left out which will be used later to test the final classification accuracy and does not enter the feature selection process. The N-1 other blocks enter the RFA process (right box) to define the optimal set of features, which will be used to build the model: the inner CV tests an SVM model built on N-2 blocks, leading to a value for the global accuracy (sum of the accuracies obtained for each binary comparison). This inner CV loop is repeated until the accuracy curve starts to decrease and hence a maximum value of global accuracy is reached, corresponding to an optimal subset of variables. N represents the number of blocks, $n_{min}$ (respectively $n_{max}$) represents the minimum (respectively maximum) number of selected features and $\Delta n$ the step size. Figure and caption from (Schrouff* et al, 2012).

**Classification procedure**

After feature extraction and selection, the retrieval session was modeled using binary Gaussian Processes classification (GP (Rasmussen and Williams, 2006)). In order to obtain multiclass predictions from the three binary classifiers, an error-correcting output code scheme (ECOC (Dietterich and Bakiri, 1995)) was used to assign a prediction (F, B or A) to each trial, based on the binary one-versus-one Gaussian Processes classifiers ((Schrouff* et al, 2012), Table 6). Model performance was assessed in terms of balanced accuracy (i.e. average of the class accuracies) and tested for significance using 1000 permutations.

Table 6. ECOC based on the probabilities of the three binary classifiers, one for each possible pair of categories, using predictions (left panel) or probabilities (right panel). Rows correspond to the considered categories and columns to the different binary comparisons (F faces, B buildings and A animals). An example is given in the last row, with the corresponding Euclidean distance $L_k$ (and how it is calculated in detail) between the codewords of each class and the binary predictions for the example data point. The class leading to the smallest distance $L_k$ is associated to the data point (in our example buildings, in bold text). k ranges from 1 to K, the number of classes.

| Category | Prediction codeword | | | Probability codeword | | | Example $L_k$ and computation |
|---|---|---|---|---|---|---|---|
| | F-B | F-A | B-A | F-B | F-A | B-A | |
| Faces | 1 | 1 | 0 | 1 | 1 | 0.5 | $L_1 = 1.4 = \|1-0.2\|+\|1-0.6\|+\|0.5-0.7\|$ |
| Buildings | -1 | 0 | 1 | 0 | 0.5 | 1 | $L_2 =$ **0.6** $= \|0-0.2\|+\|0.5-0.6\|+\|1-0.7\|$ |
| Animals | 0 | -1 | -1 | 0.5 | 0 | 0 | $L_3 = 1.6 = \|0.5-0.2\|+\|0-0.6\|+\|0-0.7\|$ |
| Example values | | | | 0.2 | 0.6 | 0.7 | |

The model was then applied to the 4 rest sessions, in order to compute the proportions of scans during which task-specific activity patterns were reinstated. Modeling spontaneous brain activity, i.e. rest sessions, is a challenge for two main reasons.

The first challenge is the absence of a ground truth: there are no means of checking the accuracy of the predicted output. To solve this issue, we used the confidence of the classifier rather than its predictions. We indeed assumed that if a scan was strongly linked to the task the model was

built for, the classifier would be more confident about its prediction than about a random prediction. This confidence measure allowed assessing scans which were significantly linked to the task. The confidence of the classifier was assessed by the distance (named L) between the two most probable categories, in terms of distances to the codewords (Dietterich and Bakiri, 1995). Finally, to compare the memory and control conditions, each rest session was summarized by only one number.

The second challenge is finding a baseline to compare with. We solved this issue also by permuting confidence measures. More specifically, the model built on the retrieval session (i.e. the three binary GP classifiers computed from the retrieval session) was applied to each scan of the rest sessions. Thereby, each scan was classified as being closer to either the pattern of retrieving a picture of a face, of a building or of an animal. No other choice is possible in view of how our model was defined (i.e. no comparison with a rest condition). Since each scan is associated with a label (i.e. face, building or animal), we needed to distinguish the scans that were classified randomly (i.e. each binary classifier led to a low probability associated with the prediction, probably close to 50%) from those that were classified more confidently (i.e. each binary classifier led to a high probability associated with the prediction).

In this sense, the ECOC approach was used to associate a label to each scan and also to assess the confidence of the prediction by taking the distance between the two most probable classes (in terms of distance to the ECOC table, Table 6). A unique measure, referred to as L, is therefore attributed to each scan and is computed as:

$$L = L_{k1} - L_{k2}$$

with $L_{k1} = \max_{k=1\ldots K} L_k$ and $L_{k2} = \max_{k=1\ldots K \setminus k1} L_k$, the difference between the two most probable classes, with k being the number of classes. In the example of Table 6, $L = |1.4-0.6| = 0.8$. For each prediction, the baseline level of L was then computed using 1000 permutations of the true training labels.

The labels of the training set were then randomly shuffled, resulting in one value of L per scan and permutation ($L_i$). As in the correction for multiple comparisons, the maximum value of L was then selected for each permutation ($L_p$) which allowed comparing the L value of each scan ($L_i$) to the 1000 L values of the permutations (Figure 31).

The proportion of scans linked to the memory task, further referred to as Pr, was then computed as the percentage of scans for which the associated p-value was <0.05. The classification procedure of the retrieval and rest sessions is illustrated in Figure 32.

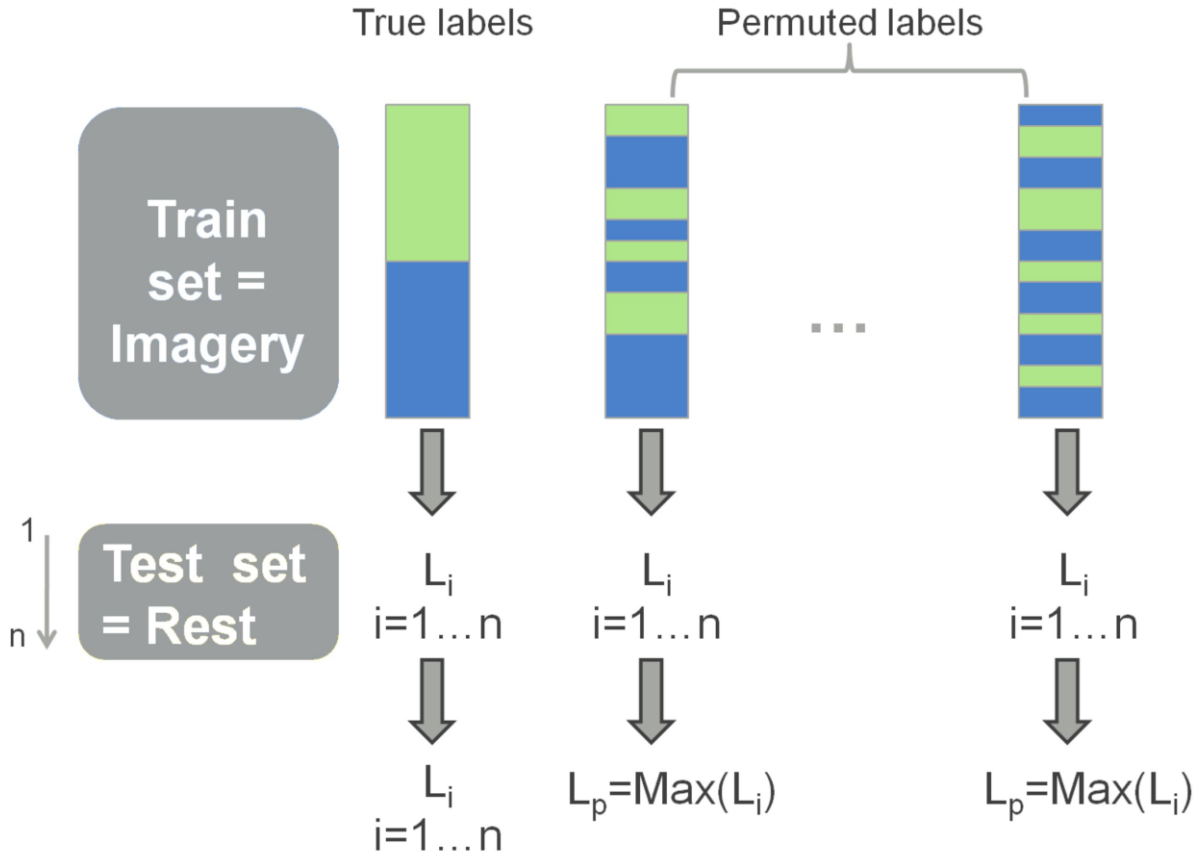


Figure 31. Assessing the significance of L. L was first computed for each scan using the true labels. The labels of the training set were then randomly shuffled, resulting in one value of L per scan and permutation ($L_i$). As in the correction for multiple comparisons, the maximum value of L was then selected for each permutation ($L_p$) and compared to the L values obtained from the true labels

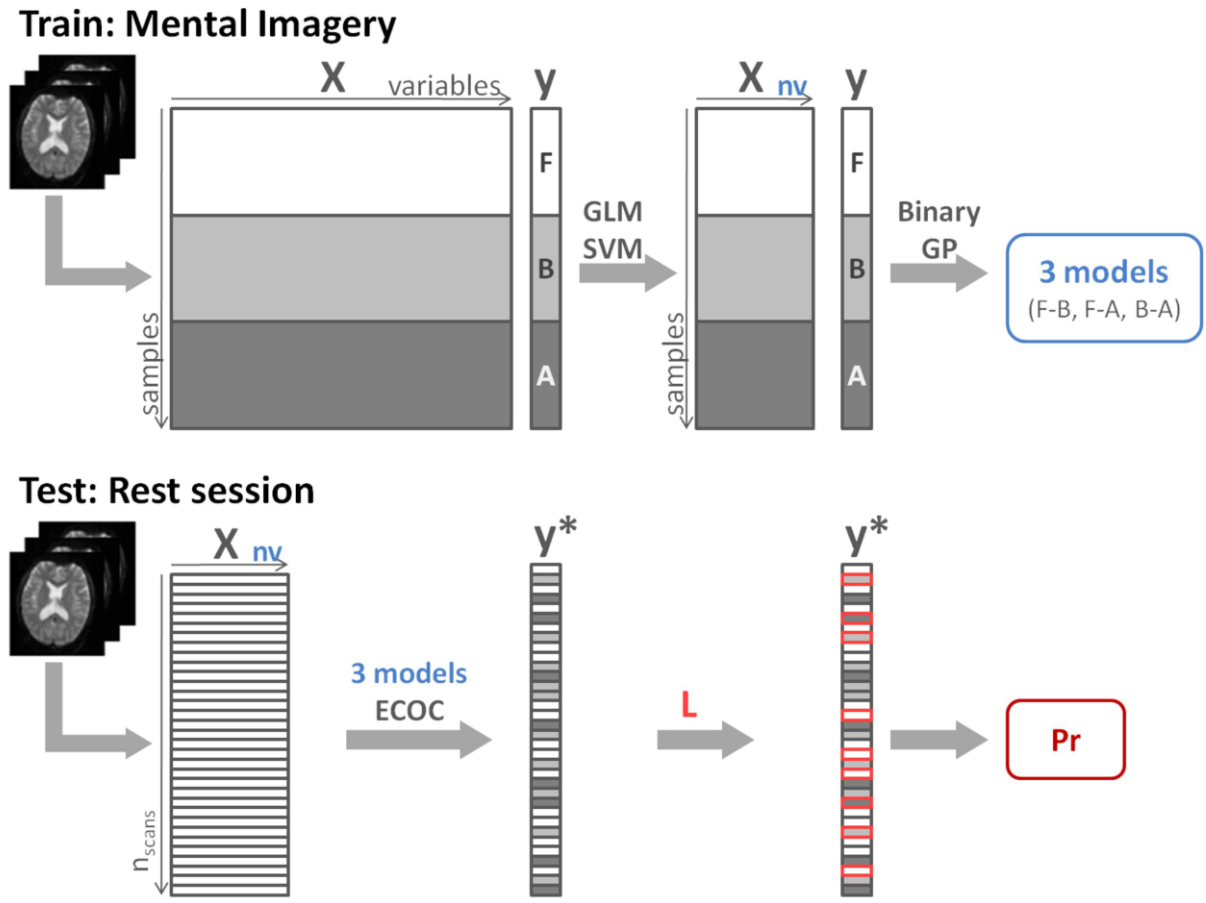


Figure 32. Machine learning modeling of resting state fMRI data. During the training phase, univariate and multivariate feature selection techniques (GLM and SVM) were used to select a subset of the input voxels/variables nv. GP binary models were then built to discriminate between the three categories, i.e. F, B and A. The testing set corresponded to the sessions of resting state wakefulness. In this case, the nv variables were selected before applying the previously built models to the rest sessions, from which we computed a value of confidence L for each scan. Using permutations, the L value allowed computing which scans were significantly linked to the task (framed in red), and hence their proportion Pr thereby summarizing the rest session into a unique number.

**Detecting memory traces**

To support the theory of memory consolidation, we should observe a different change in Pr from pre-task to post-task rest between the memory and control conditions. For each subject, a one-tailed Wilcoxon signed rank test assessed the significance of the difference between the two conditions at the group-level (memory>control):

$\Delta Pr_m - \Delta Pr_o > 0$

with $\Delta Pr_m = Pr_{R2m} - Pr_{R1m}$ and $\Delta Pr_o = Pr_{R2o} - Pr_{R1o}$ the difference in Pr from pre-task ($Pr_{R1m}$ and $Pr_{R1o}$) to post-task rest ($Pr_{R2m}$ and $Pr_{R2o}$), respectively.

We also checked whether task-related reactivations were not related to active rehearsing of the learned material during resting fMRI sessions, despite the experimental instructions.

**Relationship with behavioral measure**

The subjects' behavioral performance d' (Green and Swets, 1966) in terms of content of the images (derived from the recognition task following the experiment) was correlated with the increase in Pr from pre-task to post-task rest session ($\Delta Pr$) in both the memory and control conditions. We hypothesized that a positive correlation in the memory condition would be in support of the memory consolidation theory: the higher the proportion of scans significantly related to the task $Pr_m$, the higher the performance d' would be.

The values obtained for the correlation rho, as well as their difference, were then compared to correlation coefficients obtained from random permutations of d' across subjects. 1000 Permutations were performed, giving a null distribution for correlation coefficients in the memory and control conditions as well as for their difference.

**Temporal evolution**

We also assessed the duration of reactivations. We defined an episode as one or more successive scans which are significantly linked to the task. This made it possible to compute their duration and their proportion (compared to the total number of scans linked to the task). The threshold of minimum duration was varied from 1 to 10. The proportion of episodes with a minimum duration equal or larger than the threshold could then be computed, as well as their average duration. To reveal population effects, the proportion and average duration of the episodes were averaged across subjects. Finally, a Friedman test assessed

the significance of the difference between the memory and control conditions (by subtracting the pre-task from the post-task value).

The order of the memory and control condition was counterbalanced across participants, which could affect the spontaneous activity during the rest sessions of the control condition. This was tested as well.

**Phase information**

Finally, we estimated whether the phase structure implemented in the experimental design influenced the temporal organization of the reactivations during post-learning resting wakefulness. Studying the phase information using machine learning modeling required the use of the labels associated to each scan. More specifically, we identified which transitions of the labels (i.e. from face F to building B for example) led to a scan significantly linked to the task. Using this concept, a matrix of transitions could be built for each subject and rest session. To account for the different number of scans included in the rest sessions, the number of transitions was converted into proportions of transitions, i.e. the number of transitions divided by the length of the time-series.

We then defined the forward cycle as the transitions in accordance with the temporal structure imposed during the encoding session, i.e. F-B-A-F. As a control, we also defined the reverse cycle, i.e. F-A-B-F (Figure 27 in section 4.2.5.3). The transitions following the forward or reverse cycles were then summed, to obtain two measures per subject and per rest session (Table 7), corresponding to the proportions of transitions following the forward or reverse cycle. The increases in transitions from pre-task to post-task rest sessions were then computed for both the forward and reverse cycles. We therefore obtained four values: $\Delta Pr$ for the forward and reverse cycles, in both the memory and control conditions. According to our hypothesis, we should observe a significant effect of the condition on the forward cycle, but not on the reverse cycle and this should be noticeable in the memory condition. These hypotheses were tested using Wilcoxon ranked sum test.

Table 7. Illustration of our transition matrix. Columns represent the labels associated to the scans significantly linked to the task whilst rows represent the labels associated to the scans preceding them. The transitions can then be identified in 3 categories: identical transitions (i), transitions following the forward cycle (f) and transitions following the reverse cycle (r).

| | | Scan t sign. linked to the task | | |
|---|---|---|---|---|
| | | F | B | A |
| Scan t-1 (sign. or not sign.) | F | i | f | r |
| | B | r | i | f |
| | A | f | r | i |

**Effect of the significance threshold**

In this work, most analyses result from the choice of scans defined as significantly linked to the task. More specifically, we defined a threshold to which a scan is considered as significantly linked to the task ($p<0.05$) that might affect interpretation. To ensure that our results do not spuriously result from the choice of this threshold, we computed the increases in Pr for each condition, as well as its correlation with the behavioral performance when varying the threshold from 0.01 to 0.1.

### 4.2.5.7. Software and statistical testing

Most analyses were carried out with Matlab 7.12.0 (R2011a) (Mathworks). The experimental design was coded in Cogent 2000 and Cogent Graphics (http://www.vislab.ucl.ac.uk/cogent.php). Preprocessing and univariate analysis of the images was performed using SPM8 (www.fil.ion.ucl.ac.uk/spm). Dynamic causal modeling was done with the DCM toolbox of SPM8. Cross-correlations and explained variance were coded in Matlab. Spatial networks were examined using NEDICA ((Perlbarg et al, 2008b) sites.google.com/site/netbrainwork). The SVM implementation used is the LIBSVM toolbox ((Chang and Lin, 2013) www.csie.ntu.edu.tw/~cjlin/libsvm) with a PROBID interface ((Marquand and Mourão-Miranda, 2013) www.brainmap.co.uk). The GP implementation (www.gaussianprocess.org/gpml (Rasmussen and Williams, 2006)) is also interfaced in PROBID.

Statistical tests were performed with Matlab 7.12.0 (R2011a) and SPSS 16.0. As a rule, nonparametric statistical tests were used, given the size of the dataset. Friedman tests were applied when comparing the three categories, and Wilcoxon ranked sum tests were used as binary post hoc comparisons. Correlations were verified with Spearman rank tests. Model performance was tested for significance using permutations.

## 4.3. Results

### 4.3.1. Population

Sixteen healthy, right-handed participants participated in the study (8 female, age range 19-29y). After discarding behavioral outliers, 11 participants were included in fMRI analyses (5 female, age range 21-27y, median 25; Table 8).

Five participants were excluded because of high anxiety (Beck anxiety inventory >8) and depression (Beck depression inventory >6) and because they did not comply with total abstinence from caffeine and tobacco. Moreover, one of them had a bad sleep quality (PSQI >8, sometimes taking sleeping medication); for another, some data was missing; and one participant who was an outlier on performance scores (d'), used an alphabetic code (instead of images) to mentally represent maze items. Moreover, after the debriefing, these volunteers appeared to have consciously rehearsed the task during the post-learning rest session the whole time. To avoid any confound of active rehearsal instead of memory consolidation or increased noise in the dataset, we had to exclude them.

One volunteer preferred not to complete all parts of the IPI because of personal reasons. Because all his other data was normal, he was not excluded.

### 4.3.2. Performance

All participants had an excellent retention of the experimental material in terms of discrimination index d' (Green and Swets, 1966). None had rehearsed any image in the pre-task rest session, contrary to the post-task rest

Table 8. Demographic data of included volunteers.

| demographic data | med | min | max | N |
|---|---|---|---|---|
| age | 25 | 21 | 27 | 11 |
| chronotype | 58 | 42 | 67 | 11 |
| epworth | 4 | 1 | 10 | 11 |
| PSQI | 3 | 1 | 8 | 11 |
| Beck anxiety | 3 | 0 | 8 | 11 |
| Beck depression | 2 | 0 | 6 | 11 |
| LSDQ2 | 95 | 9 | 125 | 11 |
| IPI 1: day-dreaming frequency | 43 | 16 | 59 | 11 |
| IPI 2: night dreaming frequency | 34 | 15 | 52 | 10 |
| IPI 3: absorption in DD | 47 | 32 | 70 | 10 |
| IPI 4: acceptance of DD | 45,5 | 35 | 58 | 10 |
| IPI 5: positive reactions in DD | 34 | 14 | 55 | 10 |
| IPI 6: frightened reactions to DD | 22,5 | 13 | 39 | 10 |
| IPI 7: visual imagery in DD | 35 | 27 | 58 | 10 |
| IPI 8: auditory images in DD | 27 | 19 | 56 | 10 |
| IPI 9: problem solving DD | 27 | 17 | 55 | 10 |
| IPI 10: prent-oriented DD | 34,5 | 28 | 45 | 10 |
| IPI 11: future in DD | 43,5 | 27 | 60 | 10 |
| IPI 12: past in DD | 32 | 23 | 45 | 10 |
| IPI 13: bizarre improbable DD | 34,5 | 16 | 47 | 10 |
| IPI 14: mind wandering | 37 | 20 | 44 | 10 |
| IPI 15: achievement-oriented DD | 17,5 | 12 | 49 | 10 |
| IPI 16: hallucinatory-vividness of DD | 17 | 12 | 38 | 10 |
| IPI 17: fear of failure DD | 19 | 12 | 32 | 10 |
| IPI 18: hostile DD | 18 | 12 | 27 | 10 |
| IPI 19: sexual DD | 32,5 | 13 | 54 | 10 |
| IPI 20: heroic DD | 19,5 | 14 | 32 | 10 |
| IPI 21: guilt DD | 16,5 | 12 | 25 | 10 |
| IPI 22: curiosity: interpersonal | 34 | 27 | 40 | 10 |
| IPI 23: curiosity: impersonal-mechanical | 36 | 23 | 46 | 10 |
| IPI 24: boredom | 30 | 25 | 37 | 10 |
| IPI 25: mentation rate | 41,5 | 30 | 57 | 10 |
| IPI 26: distractibility | 38,5 | 21 | 48 | 10 |
| IPI 27: need for external stimulation | 37,5 | 34 | 51 | 10 |
| IPI 28: self-revelation scale | 37 | 26 | 52 | 10 |

session in the memory condition (Table 9). Buildings were more difficult to remember (Friedman p=0.0346) than faces (post hoc Wilcoxon tests, Bonferroni corrected, p=0.0404) and animals (p=0.0066) as was also reported by the volunteers in the debriefing; however, no difference was found between faces and animals (p=1.000). In terms of the number of rehearsed items, there was a difference between categories (Friedman p=0.0116, post hoc Wilcoxon binary comparisons did not survive Bonferroni correction: FB p= 0.6261; BA p=1.000; FA p=1.000).

Table 9. Behavioral performance d' (in terms of the content of the images and of the position on the screen) of all participants for every category separately and all categories confounded, and the number of reported mentally rehearsed images during the post-task rest session. Qualitative reports were translated as: all=27, most=20, less=10, few=2 and are marked by asterisks (*).

| subject | d' content | | | | d' position | | | | # rehearsed | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F | B | A | total | F | B | A | total | F | B | A | total |
| 1 | 2,73 | 2,4 | 3,56 | 3,61 | 1,19 | 0,99 | 2,06 | 1,34 | 3 | 0 | 2 | 5 |
| 2 | 4,92 | 1,99 | 3,88 | 3,17 | 0,90 | 0,61 | 2,99 | 1,32 | 20* | 10* | 5 | 35* |
| 3 | 4,92 | 3,88 | 3,56 | 4,69 | 4,00 | 0,65 | 2,96 | 1,96 | 2* | 2* | 2* | 6* |
| 4 | 4,92 | 2,08 | 3,88 | 3,23 | 2,27 | 2,29 | 3,31 | 2,69 | 20* | 5 | 10* | 35* |
| 5 | 4,92 | 2,44 | 4,92 | 3,57 | 4,00 | 1,29 | 3,41 | 2,45 | 20 | 15 | 20 | 55 |
| 6 | 3,56 | 3,19 | 3,88 | 4,29 | 2,92 | 1,96 | 3,08 | 2,57 | 12 | 6 | 10 | 28 |
| 7 | 2,36 | 3,05 | 2,60 | 2,55 | 2,18 | 0,96 | 0,86 | 1,10 | 5 | 3 | 0 | 8 |
| 8 | 3,19 | 1,68 | 2,47 | 3,18 | 2,41 | -1,52 | 1,79 | 1,13 | 20 | 18 | 15 | 53 |
| 9 | 2,44 | 0,94 | 3,14 | 1,94 | 2,58 | 1,69 | 1,21 | 1,77 | 0 | 0 | 1 | 1 |
| 10 | 2,36 | 1,99 | 3,88 | 2,56 | 2,06 | 0,00 | 2,26 | 1,20 | 2* | 2* | 2* | 6* |
| 11 | 2,60 | 2,64 | 4,92 | 3,01 | 2,56 | 1,32 | 1,45 | 1,70 | 27 | 15 | 27 | 69 |

### 4.3.3. Stochastic DCM

We selected 3 ROIs in the right hemisphere. The xyz coordinates of the center of the spheres, each containing 27 voxels, were respectively 40,-50,-22 for the FFA; 20,-44,-14 for the PPA; and 50,-68,2 for the AA (Figure 33).

**Testing all models**

First, we tested all models with all possible connections. Bayesian model selection (random effects inference) revealed that the fully connected model was significantly the best in all rest sessions (Figure 34).

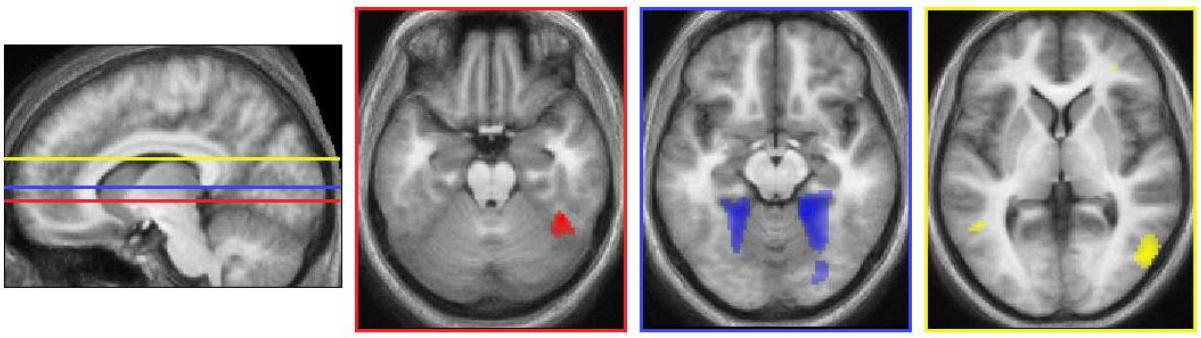

Figure 33. GLM of the exploration task on the structural template of our 11 subjects. For display purposes, the XY coordinates are X = +10 and Y= 0, uncorrected at p = 0.001. Red = faces (Z coordinate of this slice = -22), blue = buildings (Z = -14), yellow = animals (Z = +2).

**Testing families of models**

Second, the models of interest were specified into three families (Figure 28 in section 4.2.5.3). Model selection revealed that the forward model, mimicking the order that is imposed by the memory task, had the greatest evidence only during the post-learning rest session in the memory condition (Figure 35), suggesting spontaneous replay of brain activity after task learning. The backward model was the most probable during all other rest sessions (before the memory task, before and after the control task).

**Correlation with rehearsal and performance**

Third, we checked whether the connective strength between the three brain regions was related to participants rehearsing the learned material during resting fMRI sessions, despite the experimental instructions. No significant correlation was found between the number of mentally rehearsed images during the memory condition and the model parameters of the fully connected model (pre-task rho=0.4890, p=0.0760, post-task rho=0.2247, p=0.4400), nor with the forward (pre-task rho=-0.0463, p=0.8752, post-task rho=-0.2775, p=0.3367), or backward models (pre-task rho=0.0463, p=0.8752, post-task rho=0.2775, p=0.3367).

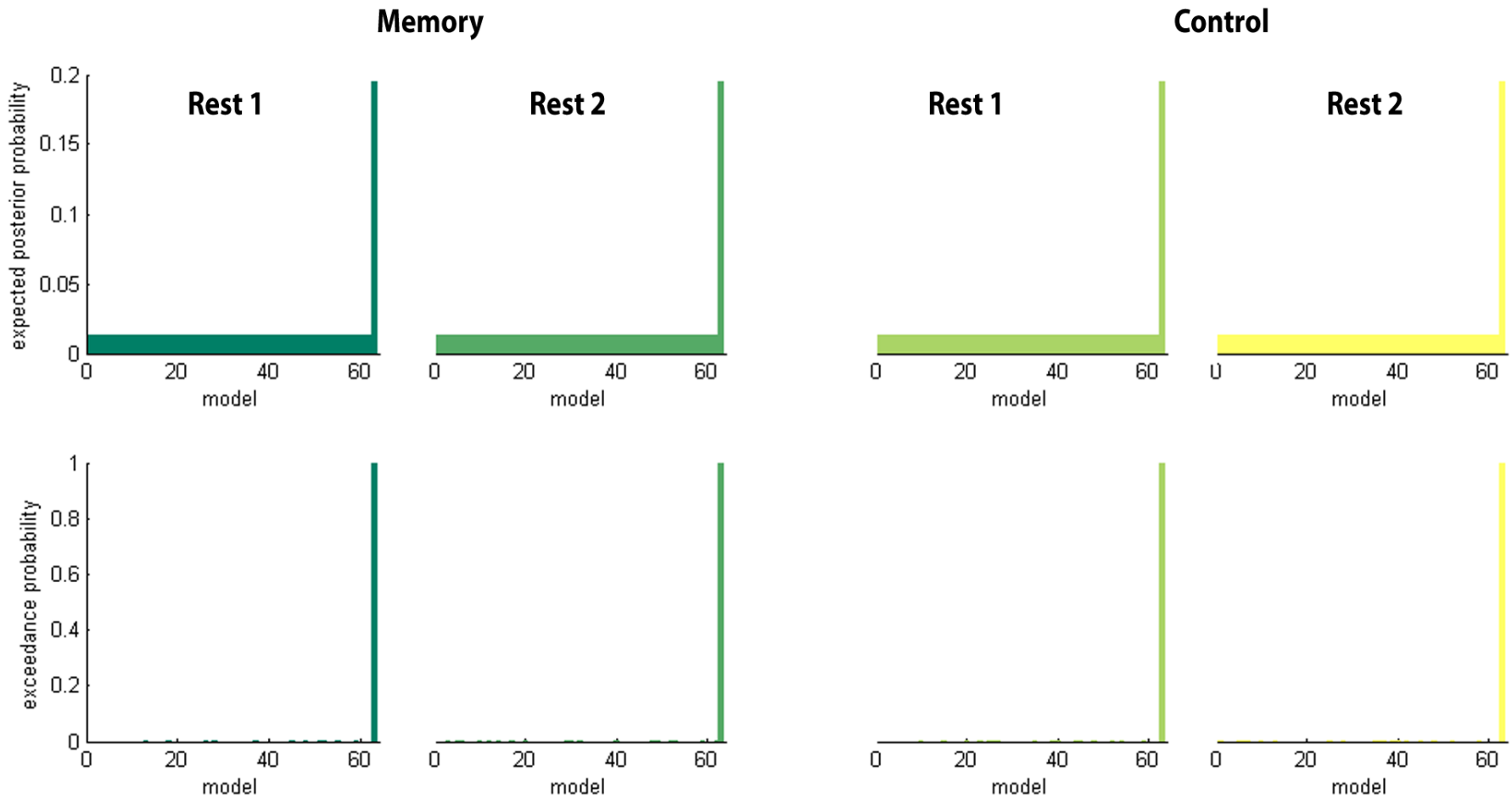


Figure 34. Random effects Bayesian model selection, expected posterior probability and exceedance probability for all rest sessions (i.e. the probability of one model being more likely than any other) show that the fully connected model (model 63) has the greatest evidence in all rest sessions. The post-task rest session in the memory condition did not differ from any other rest session.

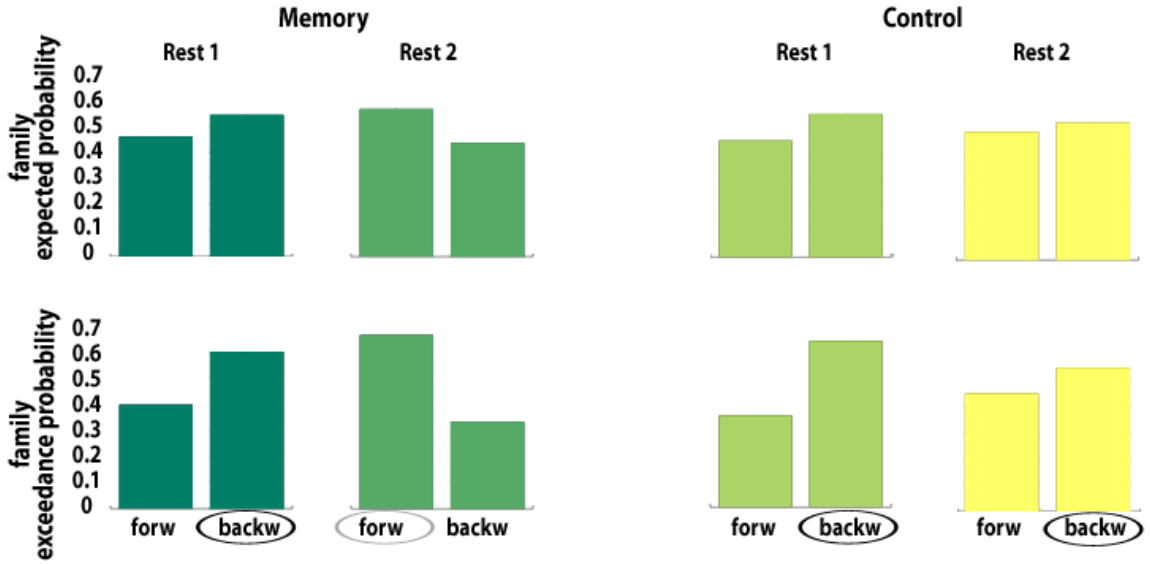


Figure 35. Familywise Bayesian model selection was used to establish the neuronal network architecture. Family expected probability and exceedance probability for all rest sessions. The backward family wins in the pre-task rest, before and after the control task (black circles). The forward family wins only in the post-task rest (gray circle).

In addition, we tested the same parameters during the control auditory task. Similar results were found (fully connected model (pre-control rho=-0.0154, p=0.9464, post-control rho=0.0749, p=0.8343), forward (pre-control rho=-0.2115, p=0.4680, post-control rho=-0.2203, p=0.4490) and backward models (pre-control rho=0.2216, p=0.4464, post-control rho=0.2203, p=0.4492)). Therefore, importantly, the increase in forward connectivity in the post-task rest session does not appear to result from active rehearsal by participants.

We then checked whether memory performance d' was related to the connective strength of the winning model in each rest session. No correlation was observed in the memory condition with the fully connected model (pre-task rho=0.0770, p=0.7936 and post-task rho=0.1540, p=0.5991), the forward model (pre-task rho=-0.0946, p=0.7477 and post-task rho=0.0132, p=0.9643) or backward model (pre-task rho=0.0946, p=0.7477 and post-task rho=-0.0132, p=0.9643). We found no correlation in the control condition with the fully connected model (pre-control rho=0.0198, p=0.9464 and post-control rho=-0.0616, p=0.8343), forward model (pre-task rho=-0.0682, p=0.8168 and post-task rho=0.4642,

p=0.0945) and backward model (pre-task rho=0.0727, p=0.8050 and post-task rho=-0.4642, p=0.0945).

The difference between the correlations was not significant either. In the memory condition there was neither a significant correlation between the number of rehearsed images and the fully connected model (rho=-0.3414, p=0.2322), forward (rho=-0.1101, p=0.7078) or backward model (rho=0.1101, p=0.7078), nor between d' and the fully connected model (rho=0.0242, p=0.9345), forward (rho=0.2860, p=0.3215) or backward model (rho=-0.2860, p=0.3215).

In the control condition, no correlation was found between the rehearsed images and the fully connected model (rho=-0.1123, p=0.7022), forward (rho=-0.1740, p=0.5519) or backward model (rho=0.1740, p=0.5519). Correlations with the discrimination index were nonsignificant as well: with the fully connected model (rho=-0.1122, p=0.7025), forward (rho=0.0902, p=0.7591) or backward model (rho=-0.0902, p=0.7591).

These results do not support a strong relationship between memory reactivation and later task performance.

### 4.3.4. Explained variance

**Voxels of interest**

We selected the same ROIs as for the DCM analysis, see 4.3.3.

**Explained variance of full time courses**

We extracted the timecourse of the 3 ROIs (Figure 36) and calculated the partial correlation and explained variance. During resting state after the memory task, 0.39% of the BOLD signal in the FFA could be explained by the task, 0.50% in the PPA and 0.49% in the AA (Figure 37).

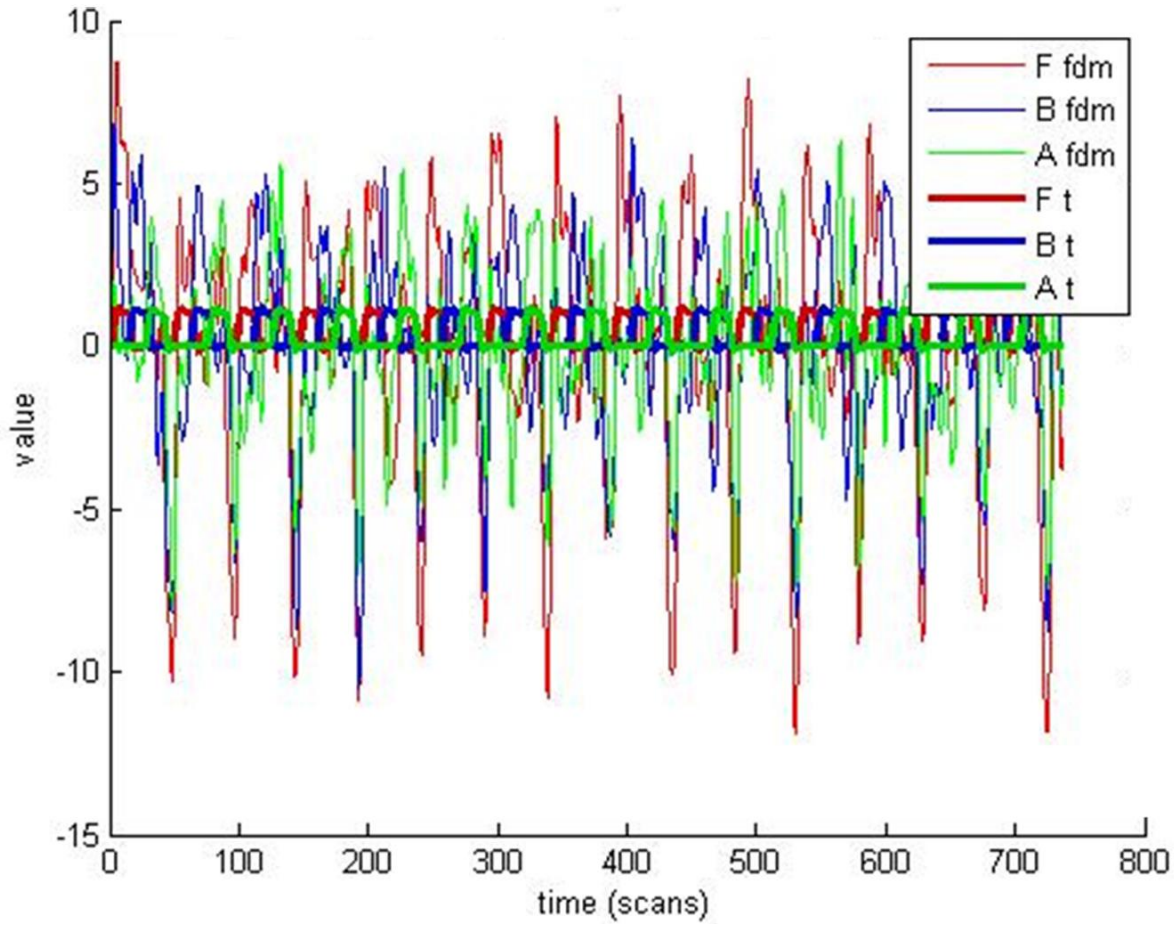


Figure 36. Example of the timecourse of one subject during maze exploration (filtered, detrended mean across all voxels in each ROI). FFA is shown in red, PPA in blue and AA in green. Bold lines indicate the theoretical BOLD signal in each region, in corresponding colors.

First, we tested whether the explained variance (EV) of the signal after task learning was significantly different from zero. Expectedly, this was the case during post-task rest ($p<0.001$). However, this was also the case during all other rest sessions ($p<0.001$ for each).

Second, we found that EV post-task rest (which is already taking into account the pre-task rest) was not different from the pre-task rest, neither in the memory condition ($p(F)=0.9476$; $p(B)=0.8438$; $p(A)=0.0356$), nor in the control condition ($p(F)=0.7928$; $p(B)=0.3579$; $p(A)=0.2122$).

Third, we examined if there was a difference between EV in the memory and control condition. This was not the case in the post-task rest sessions ($p(F)=0.8438$; $p(B)=0.1679$; $p(A)=0.3579$), and not in the pre-task rest sessions

(p(F)=1.000; p(B)=0.5994; p(A)=0.8438). Note that all values are only significant at p=0.0167 after Bonferroni correction for multiple comparisons.

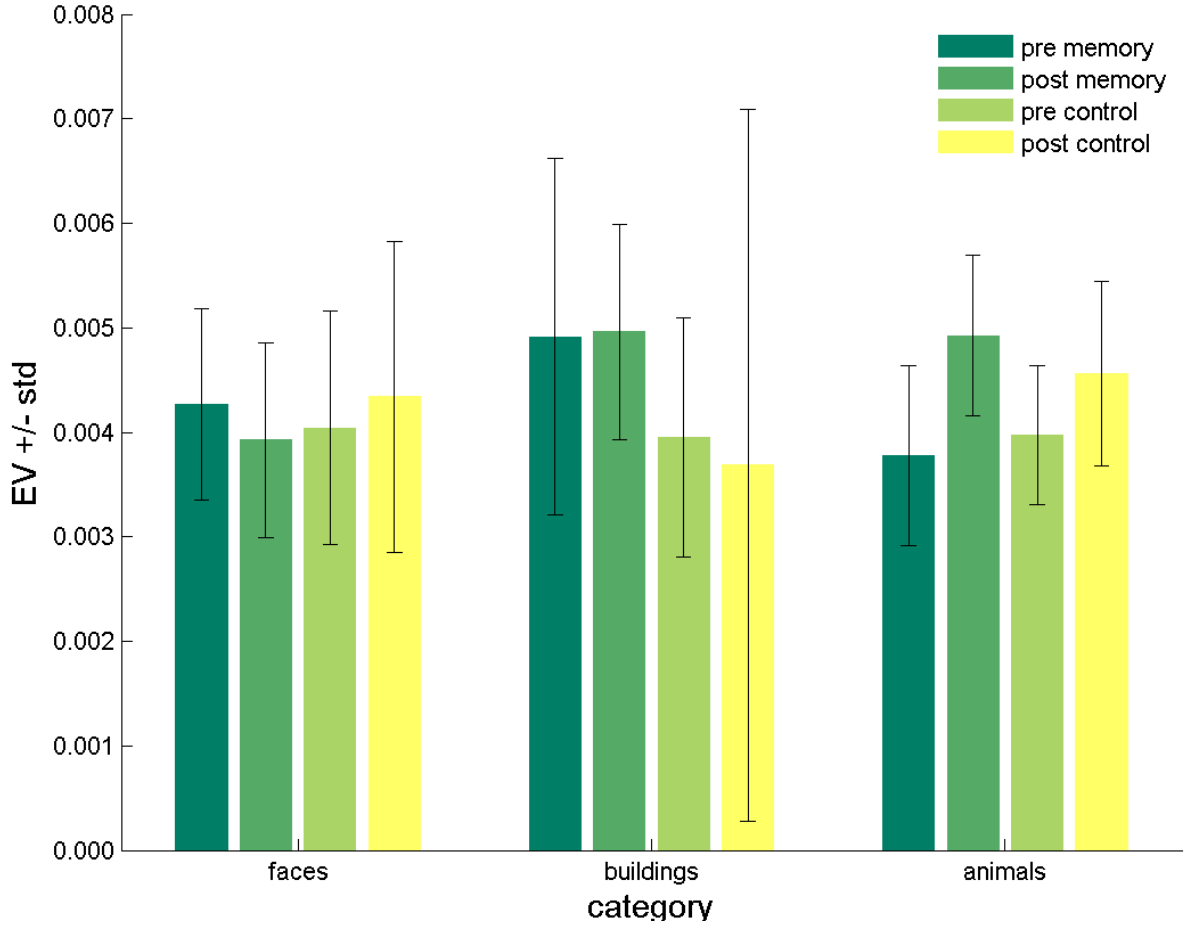


Figure 37. Explained variance and its standard deviation for the three stimulus categories (faces, buildings and animals).

**Explained variance of transition epochs**

We also considered short epochs of eight scans at the transition from one stimulus category to another. During the rest session following task learning, EV of the transition from faces to buildings was 0.95%, from buildings to animals the EV was 0.93% and from animals to faces the EV was 0.95% (Figure 38).

First, we tested whether EV of the signal after task learning was significantly different from zero. This was the case during postlearning rest ($p<0.001$) but also during all other rest sessions ($p<0.001$ for each).

Second, we found that EV post learning was not different from before learning, neither in the memory condition (p(FB)=0.7692; p(BA)=0.8973; p(AF)=0.1848), nor in the control condition (p(FB)=0.8419; p(BA)=0.3418; p(AF)=0.8053).

Third, we examined if there was a difference between EV in the memory and control condition. This was neither the case in the post-task rest sessions (p(FB)=0.6138; p(BA)=0.4047; p(AF)=0.0357), nor in the pre-task rest sessions (p(FB)=0.8787; p(BA)=0.9159; p(AF)=0.5812).

**Explained variance of flipped transition epochs**

Our third strategy consisted in computing the mirrored timecourse of the transition epochs. EV during post task rest was 0.96% for the flipped transition from faces to buildings, 0.93% for the flipped transition from buildings to animals, and 0.96% for the flipped transition from animals to faces.

We tested whether these flipped epochs were different from the normal epochs, but this was neither the case for the memory condition (p(FB)=0.9626; p(BA)=0.9532; p(AF)=0.9906) nor for the control condition (p(FB)=0.9532; p(BA)=1.000; p(AF)=1.000).

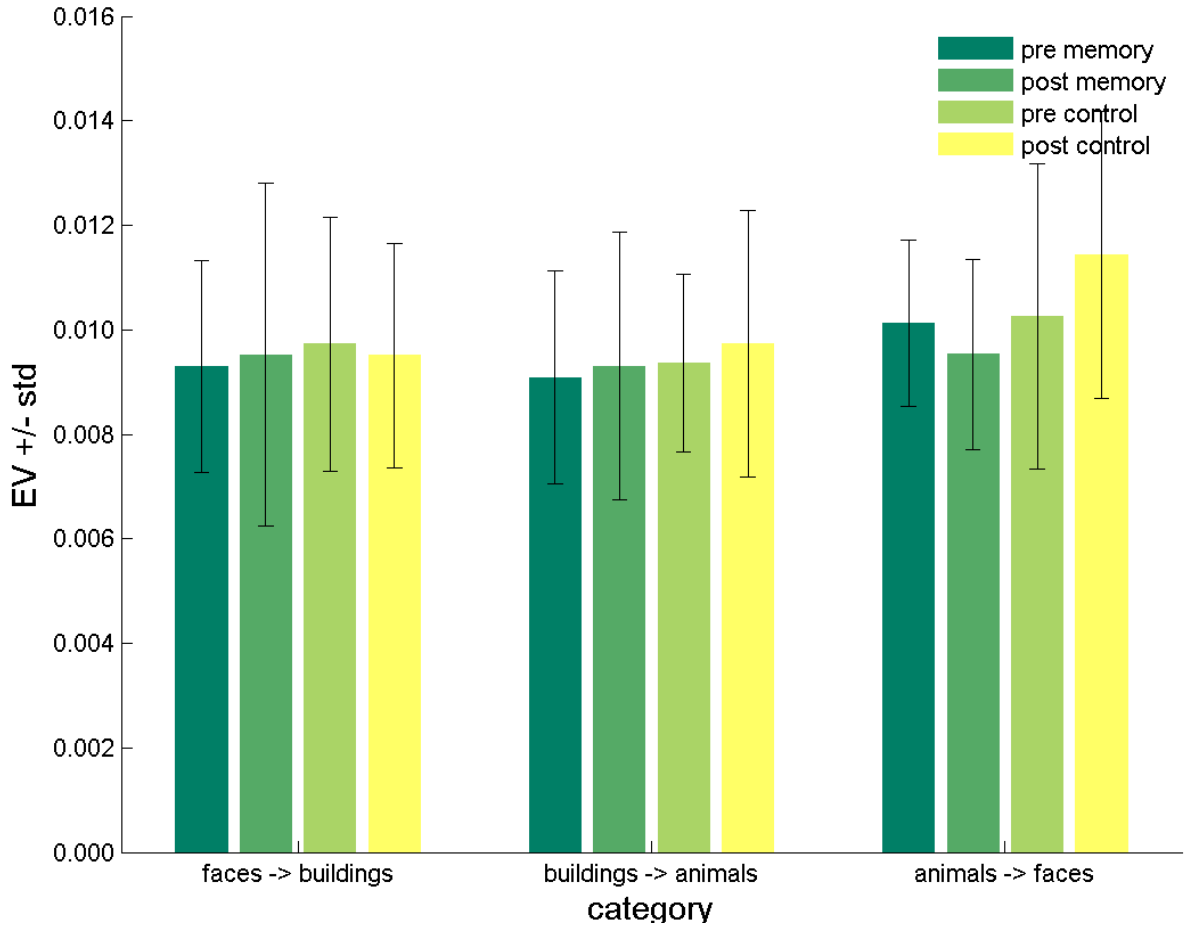


Figure 38. Explained variance and its standard deviation for the transitions between the stimulus categories (from faces to buildings, from buildings to animals, and from animals to faces).

### 4.3.5. Spatial networks identification

The results of this chapter are not yet published but are previously described in the PhD dissertation of (Schrouff, 2013).

**ROI selection**

We manually selected the ROIs of the exploration session, centered on the coordinates provided in Table 10, with two contingency layers (Figure 39). The selected ROIs define two subsets of interest: a hippocampal NOI and a maze NOI (containing FFA, PPA and AA). We also identified automatically the components according to (Smith et al, 2009). Hence, six main networks of interest were detected (Figure 40):

- Visual network (VIS): a first medial and lateral component was detected and added to the occipital component.
- Ventral attentional network (vATT): this network was found in its lateralized components (left and right), which were then merged.
- Dorsal attentional network (dATT)
- Auditory network (AUD)
- Sensori-motor network (MOT)
- Default mode network (DM)

The ROIs were then automatically selected from the thresholded t-maps. In total, 48 ROIs were considered for further analysis (57 with the manually selected ROIs).

Table 10. Coordinates of the center of the manually selected regions in the MNI space as well as their attributed names. The first three regions form the hippocampal NOI, while the six others correspond to regions activated during the display of the images ("maze" NOI). "sym" refers to the symmetry in the definition of the ROIs.

| Region | | Name | x | y | z |
|---|---|---|---|---|---|
| Left | Hippocampal 1 | L-Hipp1 | -316.800 | -68.203 | -198.439 |
| Left | Hippocampal 2 | L-Hipp2 | -178.200 | -143.187 | -144.224 |
| Right | Hippocampal | R-Hipp | 297.000 | -128.849 | -245.867 |
| Left | FFA | L-FFA | -376.200 | -522.694 | -158.875 |
| Right | FFA (sym) | R-FFA | 396.000 | -493.630 | -160.329 |
| Left | PPA | L-PPA | -217.800 | -432.144 | -96.122 |
| Right | PPA (sym) | R-PPA | 198.000 | -432.144 | -96.122 |
| Left | Animals | L-AA | -435.600 | -491.111 | -109.992 |
| Right | Animals | R-AA | 495.000 | -657.856 | 51.343 |

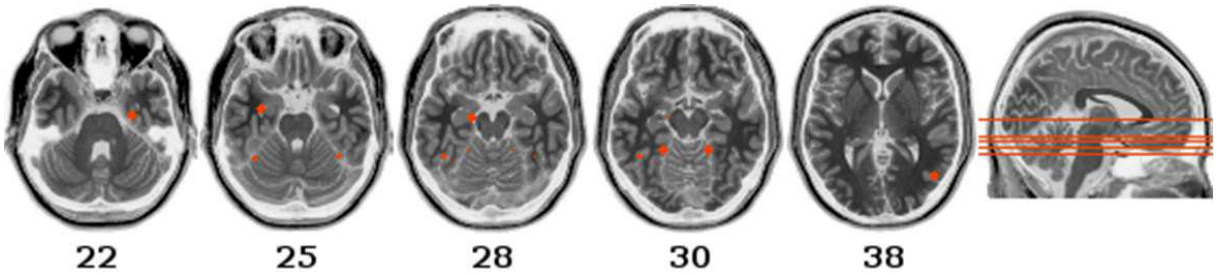


Figure 39. Manually selected regions of interest from the statistical peaks of a GLM of the exploration session. Three regions were selected in the hippocampus and six in the neocortex.

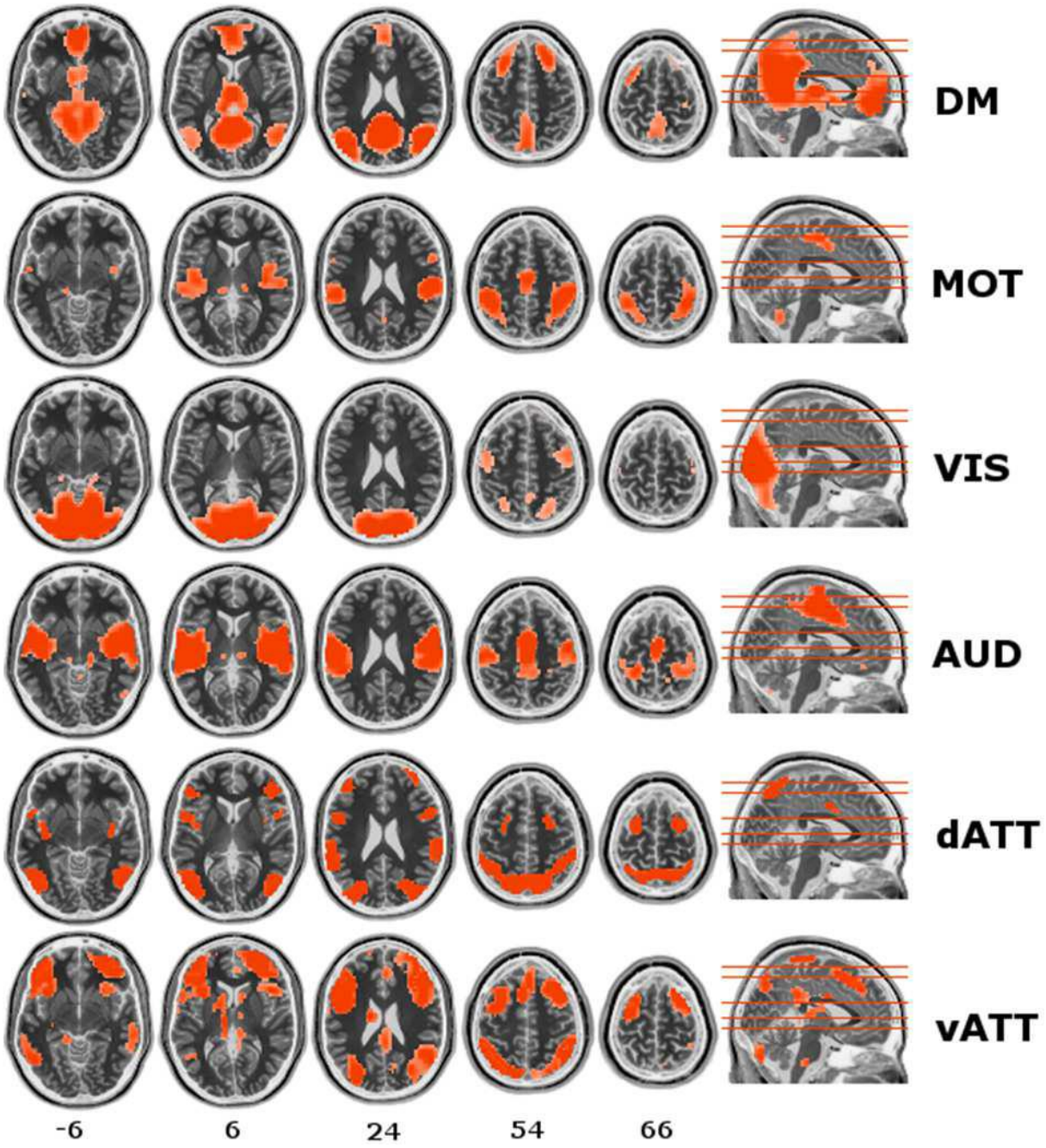


Figure 40. Automatically selected networks of interest. The t-maps display the 6 detected networks computed with $p<0.05$ with correction for multiple comparisons, at different locations on the z-axis (coordinates are shown below the slices). DM: default mode, MOT: sensori-motor, VIS: visual, AUD: auditory, dATT: dorsal attention, vATT: ventral attention network.

**Integration**

Both conditions show a significant increase in total integration. This increase is larger for the control condition (increase = 1.2484) than for the memory condition (increase = 0.4429; $p = 0.035$).

With respect to within-network integration, significant increases were observed for the VIS and AUD NOIs for the memory condition. For the control condition, significant increases were found for the DM, dATT and MOT NOIs (marked by black asterisks in Figure 41). Please note that the only significant differences between conditions were found for the DM and MOT NOIs (marked by yellow asterisks in Figure 41). An interesting and unexpected result is that no increase in within-NOI integration could be found for the Hipp and Maze NOIs in the memory condition as compared to the control condition.

All pairwise between-NOI integrations are reported in Figure 42 (significant differences between pre-task to post-task rest sessions being marked by an asterisk). The results show that the vATT and dATT NOIs were the most affected by the tasks. Although this could have been expected (Smith et al, 2009), increases in integration between the Hipp and Maze NOIs were also expected, or between the Hipp and VIS NOIs in the memory condition, which are not present. Furthermore, some results are surprising, such as the significant increases in integration between the DM and vATT NOIs, and between the DM and Hipp NOIs for the memory condition. According to (Smith et al, 2009), the DM network should not be affected by any of the considered tasks.

We were not only interested in the differences between the pre-task and post-task rest sessions. A second important point is the difference between conditions, i.e. are the increases in between-NOIs integration larger for the memory or the control condition? The p-values of these comparisons are represented in Table 11.

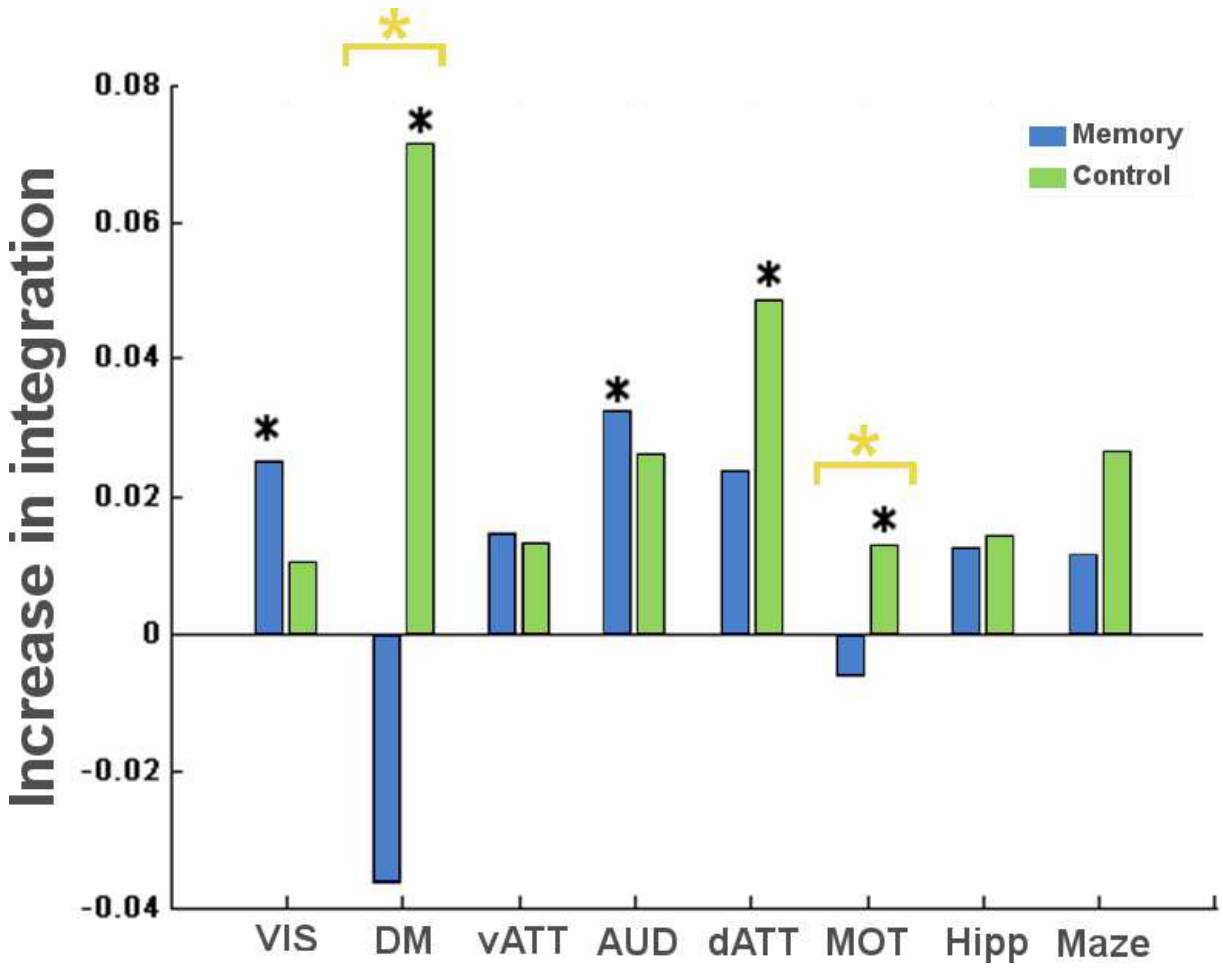


Figure 41. Within-NOI integration. Increases in within-NOI integration from the pre-task to the post-task rest session for the memory (blue) and control (green) conditions. Significant increases are marked by a black asterisk, while yellow asterisks represent a significant difference between both conditions.

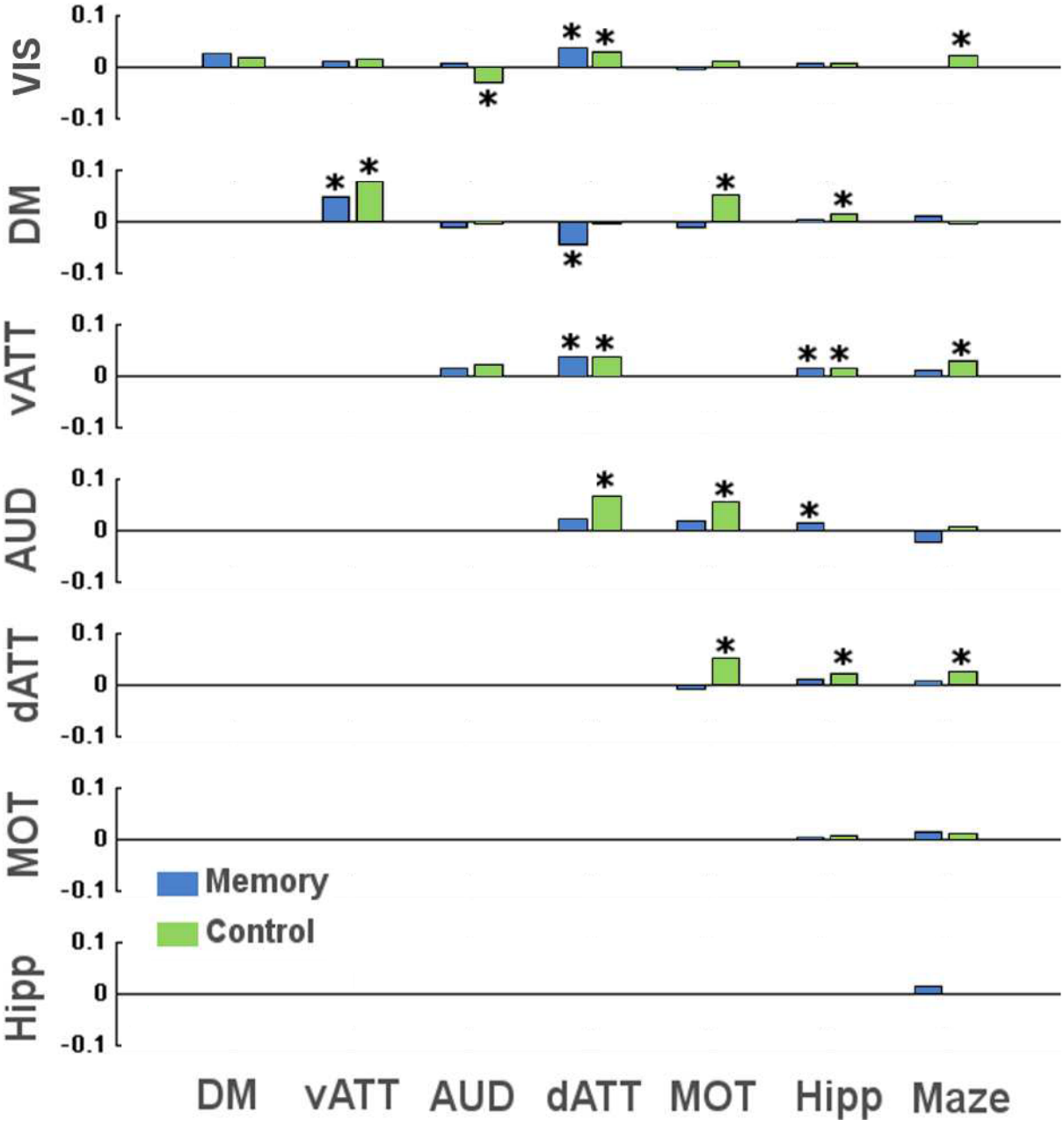


Figure 42. Between-NOI integration. Increases in between-NOI integration from the pre-task to the post-task rest session for the memory (blue) and control (green) conditions. Significant increases are marked by an asterisk.

Table 11. P values assigned to the differences between memory and control conditions for each of the pairwise between-NOI integrations. Significant results are highlighted: p>0.9 means a higher increase in the memory condition (highlighted in blue); p<0.1 means a higher increase in the control condition (highlighted in green).

| NOI | DM | vATT | AUD | dATT | MOT | Hipp | Maze |
|---|---|---|---|---|---|---|---|
| VIS | 0.651 | 0.434 | **0.966** | 0.634 | 0.135 | 0.460 | 0.127 |
| DM | | 0.272 | 0.406 | **0.071** | **0.081** | 0.154 | 0.802 |
| vATT | | | 0.357 | 0.512 | 0.488 | 0.509 | 0.195 |
| AUD | | | | 0.116 | 0.101 | **0.907** | 0.194 |
| dATT | | | | | **0.016** | 0.219 | 0.137 |
| MOT | | | | | | 0.305 | 0.612 |
| Hipp | | | | | | | 0.402 |

**Partial correlation**

The partial correlation measure was used to assess any change in connectivity between the Hipp NOI and all other NOIs (i.e. modification in partial correlation between the 3 hippocampal ROIs and any other ROI). As shown in Figure 43, the effect of the task on the hippocampal connectivity is small. Furthermore, this effect is the same for both the memory and the control conditions, leading to equal values of the integrated difference in partial correlation: IDPC(memory)=0.0084 and IDPC(control)=0.0090.

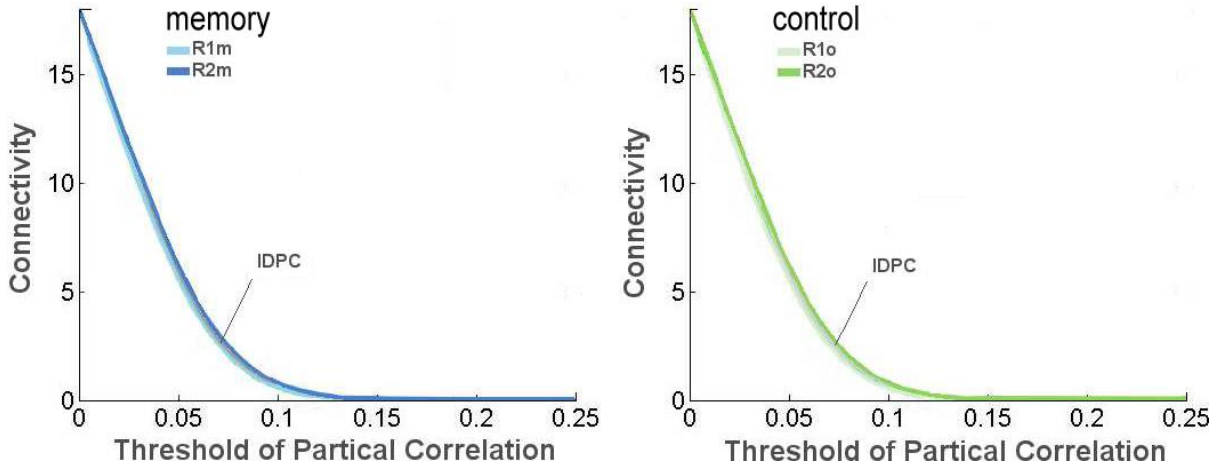


Figure 43. Connectivity of the 3 hippocampal ROIs for the memory (left) and control (right) conditions. The pre-task connectivity is plotted in light blue or green while the post-task connectivity is displayed in darker blue or green, for the memory and control conditions respectively. A small difference can be observed for both conditions, leading to small and almost equal values of the IDPC (gray area between the two curves).

### 4.3.6. Multivariate pattern analysis

**Signal extraction**

The number of extracted events from the mental imagery session and their corresponding duration were variable depending on the volunteers' ability to retrieve the different images forming the requested mental path (Table 12). These findings were consistent with the participants' performance d': the number of events is significantly lower for the buildings category than for the other two categories (Friedman test $p=0.0054$, Post hoc Wilcoxon tests, $p<0.05$, Bonferroni corrected for multiple comparisons) whereas no significant difference was detected between the number of events in the faces and animals categories ($p=0.0347$, does not survive the Bonferroni correction). This result potentially affects the classification based on fMRI data as it relies on binary comparisons. It should be noted that no direct interaction could be detected between the performances of the participant and the number of events in each category (correlations $p>0.05$).

Table 12. Number of extracted events for the mental imagery session. Percentages are in brackets and show the possible imbalances between categories.

| subject | F | | B | | A | | total |
|---|---|---|---|---|---|---|---|
| 1 | 69 | (44.23%) | 30 | (19.23%) | 57 | (36.54%) | 156 |
| 2 | 76 | (55.07%) | 11 | (07.97%) | 51 | (36.96%) | 138 |
| 3 | 47 | (30.32%) | 58 | (37.42%) | 50 | (32.29%) | 155 |
| 4 | 74 | (39.36%) | 42 | (22.34%) | 72 | (38.30%) | 188 |
| 5 | 70 | (41.42%) | 36 | (21.30%) | 63 | (37.28%) | 169 |
| 6 | 67 | (38.29%) | 44 | (25.14%) | 64 | (36.57%) | 175 |
| 7 | 18 | (21.69%) | 32 | (38.55%) | 33 | (39.76%) | 83 |
| 8 | 37 | (45.68%) | 20 | (24.69%) | 24 | (29.63%) | 81 |
| 9 | 69 | (41.07%) | 31 | (18.45%) | 68 | (40.48%) | 168 |
| 10 | 55 | (32.54%) | 58 | (34.32%) | 56 | (33.14%) | 169 |
| 11 | 77 | (38.89%) | 53 | (26.77%) | 68 | (34.34%) | 198 |
| mean | 59.29 | (39.17%) | 38.50 | (25.44%) | 53.57 | (35.39%) | 151.36 |

**Feature selection**

The mean number of extracted features was 268.79, standard deviation 179.79. The number for each participant

separately is displayed in Table 13. The high standard deviations in the number of selected voxels indicate a high variability across blocks for the retrieval session, which is caused by the design of the session.

The selected voxels were located in occipito-temporal areas (from primary areas to lingual and fusiform gyri), parahippocampal gyri and hippocampus as well as medial parietal regions (Figure 44). This was expected because activation in these areas represented properly the different aspects of the task (visual properties, spatial features and navigation).

| subject | mean | SD |
|---|---|---|
| 1 | 254 | 173 |
| 2 | 258 | 150 |
| 3 | 272 | 185 |
| 4 | 297 | 163 |
| 5 | 278 | 204 |
| 6 | 306 | 190 |
| 7 | 148 | 185 |
| 8 | 304 | 222 |
| 9 | 294 | 183 |
| 10 | 326 | 227 |
| 11 | 205 | 165 |
| mean | 268.79 | 179.79 |

Table 13. Number of RFA selected features for the mental imagery session. The optimal subset of variables is represented for each participant by its mean size and standard deviation across the number of features obtained after each cross-validation step. The last row gives the mean and standard deviation across all participants.

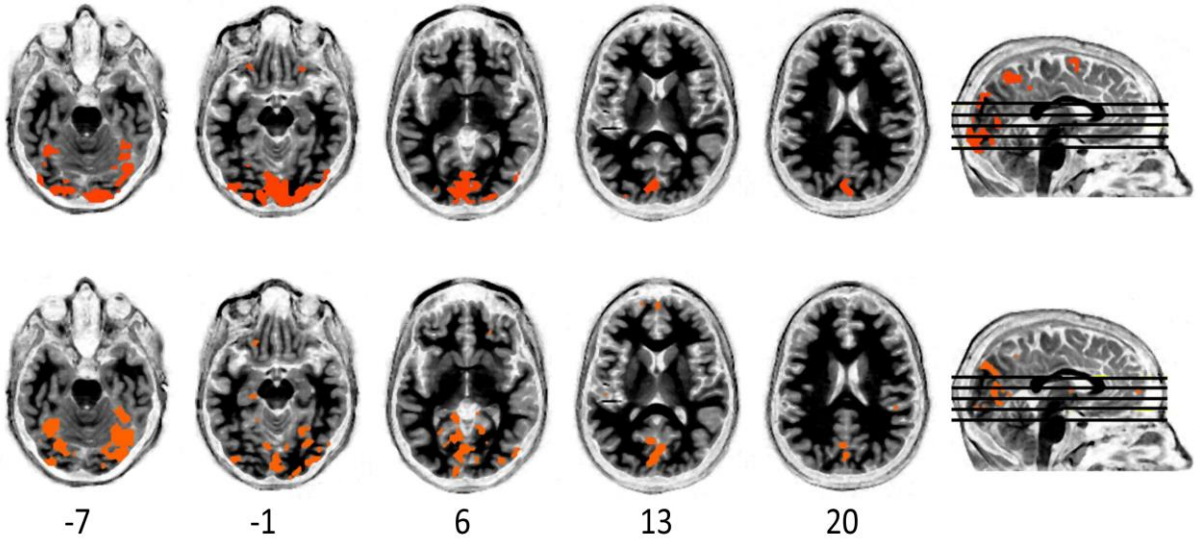


Figure 44. Voxels selected after the univariate and multivariate feature selection steps during the encoding of the memory task (top) and during the retrieval task (bottom), for one participant. Z-coordinates of the slices are displayed below the slices.

**Classification procedure**

The ECOC scheme, based on binary one-versus-one GP classifiers, was used to assign a prediction (F, B or A) to each trial (Figure 45).

For the retrieval session, data of 9 participants out of 11 could be modeled with accuracy significantly above chance level (as estimated through a permutation procedure, see (Schrouff* et al, 2012) for the technical details), with a mean balanced accuracy (i.e. the mean across blocks and significance for each participant) ranging between 32.55% (not significant) and 69.78%. The results of the modeling of the brain activity during encoding and retrieval are presented in Figure 46.

To model the rest sessions, we computed for all sessions the confidence of the prediction based on the difference between the two most probable classes (value L, computed using 1000 permutations of the true labels). An example of this distribution is shown in Figure 47.

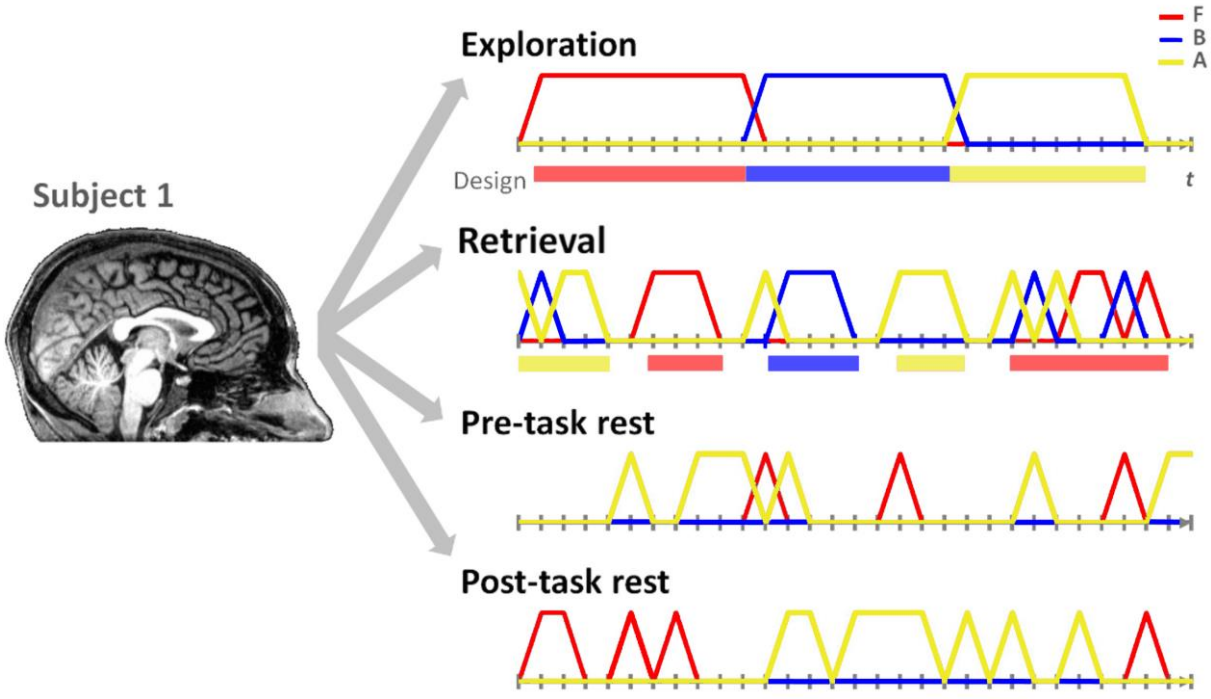


Figure 45. fMRI decoding results. For each session performed by participant 1, the multiclass predictions of the machine learning model are illustrated for F (red), B (blue) and A (yellow). The display shows 30 scans, taken from the first block in each session (exploration, retrieval) or simply as the 30 first scans (rest).

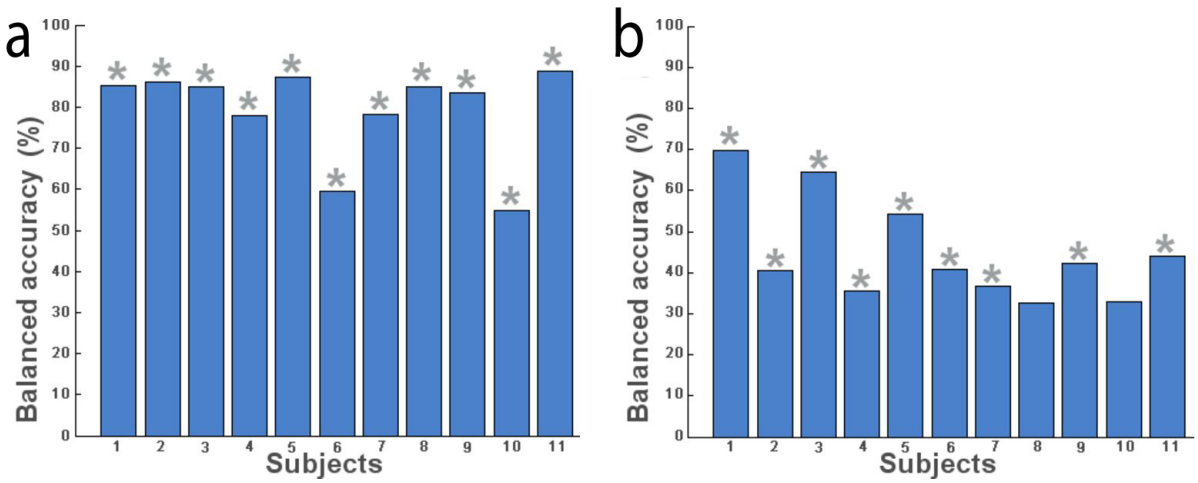


Figure 46. Balanced accuracies for brain activity during encoding and retrieval. Averages across blocks of the balanced accuracy of within-subject modeling of constrained (encoding, a) and semi-constrained (retrieval, b) brain activity. Significant results, as assessed by permutations, are marked by stars *.

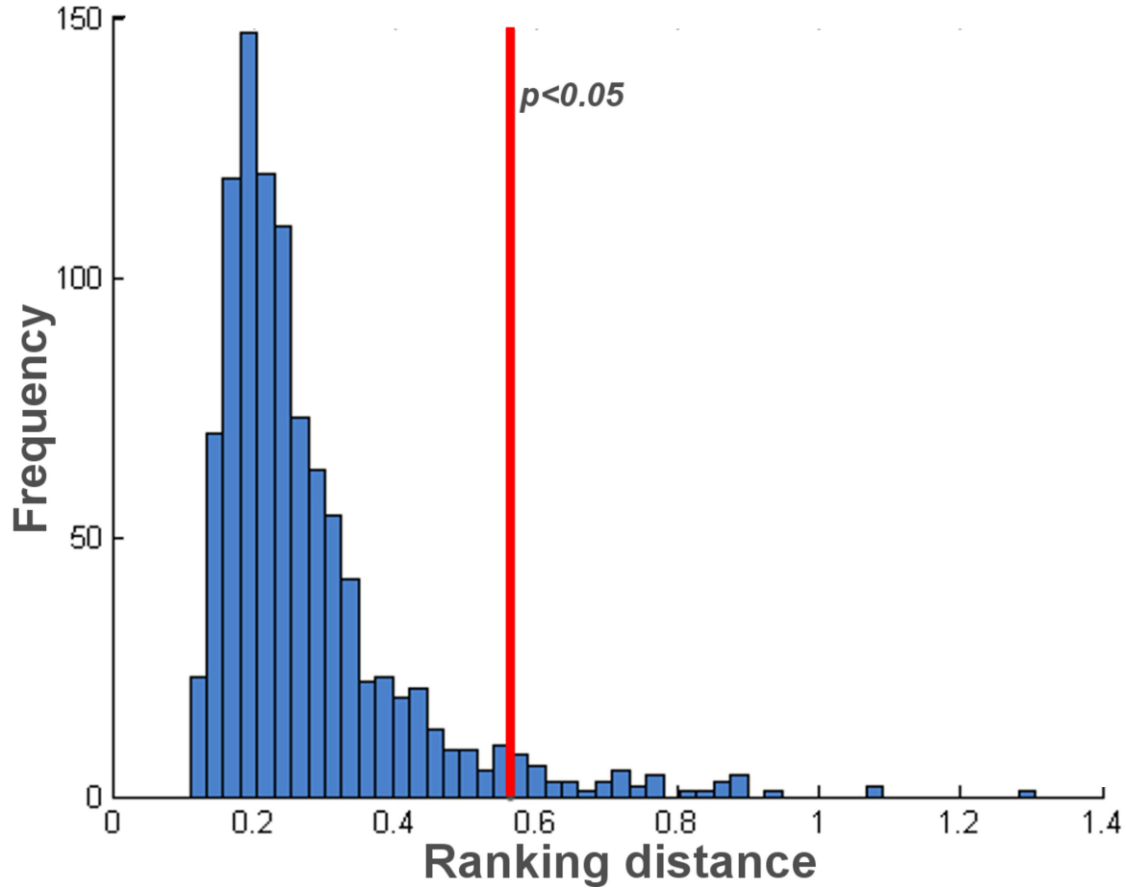


Figure 47. Example of the results of machine learning modeling of resting state fMRI data. Histogram of Lp for rest session 1 (R1m) and subject 1 using 1000 permutations, showing the non-normal distribution of the data. If L (computed using the true labels) was larger than 0.57 in this example, the corresponding scan was assessed as significantly ($p<0.05$) linked to the memory task and accounted for in the computation of Pr.

**Detecting memory traces**

The classification model built on the retrieval session was then applied to the 4 rest sessions for each subject (Figure 45), allowing us to compute the proportions of scans during which task-specific activity patterns were reinstated (Pr). These proportions Pr had non-null values for each rest session and subject (Figure 48a; Table 14; Table 15). This result suggests that brain activity continuously and spontaneously reinstates a repertoire of varied activity patterns which correspond to complex visual representations (i.e., in this instance, faces, buildings, animals). Importantly, although Pr did not significantly change between pre- and post-task rest sessions (Figure 48a), the increase in Pr from pre-task to post-task rest in the memory condition was significantly larger than in the control condition ($p=0.0293$, one-tailed Wilcoxon test; Figure 48b).

We checked whether these reactivations were not related to participants rehearsing the learned material during resting fMRI sessions, despite the experimental instructions. No significant correlation was found between the Pr increase in the memory condition and the number of mentally rehearsed images ($rho=-0.0661$, $p=0.847$). In addition, the same patterns were observed in the rest session following the oddball task, although the latter did not include any visual stimulus. Therefore, the increase in proportions of scans significantly associated with learning in the memory condition does not appear to result from active rehearsal by participants.

Although the order of the memory and control task was counterbalanced across participants, no difference was found between these two groups in terms of activity during the rest sessions in the control condition.

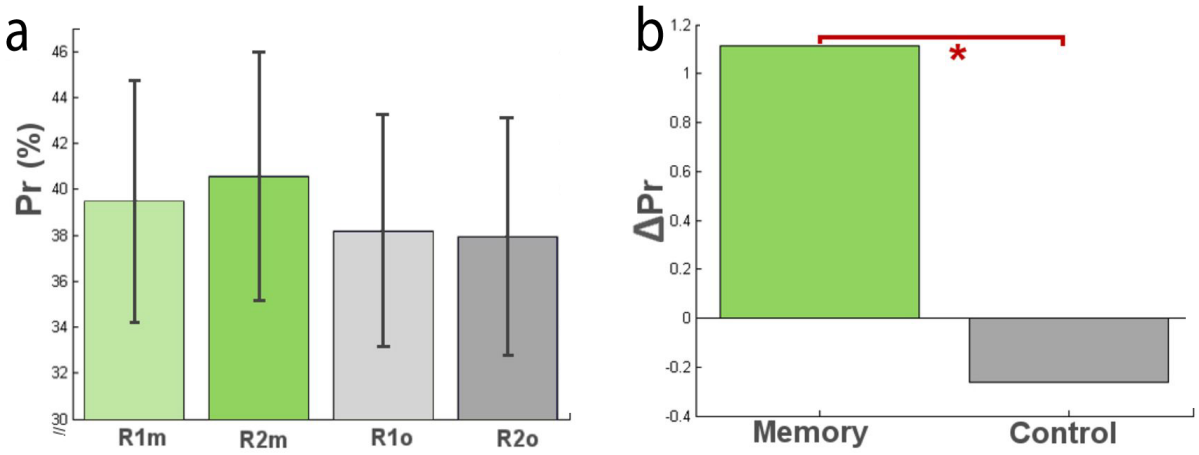


Figure 48. Detecting and characterizing mnemonic traces. a. Pr for each session in %. b. ΔPr from the pre-task to the post-task rest session (in %) for both conditions.

Table 14. Differences between the memory and control conditions in terms of 1) proportions of scans significantly linked to the task (Pr); 2) correlation (rho with associated p-value) between the subjects' behavioral performance d' and ΔPr; and 3) forward and reverse cycles as estimated by the proportions of transitions according to a F-B-A or F-A-B phase. The difference between the memory and control conditions is expressed in terms of nonparametric p-values.

| Measure | Memory condition | Control condition | Difference p-value |
|---|---|---|---|
| ΔPr (%) | 1.1136 | -0.2636 | 0.0293 |
| rho (ΔPr, d') | 0.4968 (p=0.0580) | -0.0137 (p=0.5040) | 0.0400 |
| Forward cycles (in %) | 0.3311 | -0.6536 | 0.0305 |
| Reverse cycles (in %) | 0.0000 | -0.3257 | 0.2179 |

Table 15. Proportions Pr of scans significantly linked to the task for each participant and rest session. Increases from the pre-task to the post-task rest sessions are reported under ΔPr(m/o).

| subject | R1m | R2m | ΔPr(m) | R1o | R2o | ΔPr(o) |
|---|---|---|---|---|---|---|
| 1 | 381.107 | 384.365 | 0.3257 | 400.651 | 387.622 | -13.029 |
| 2 | 195.440 | 172.638 | -22.801 | 140.065 | 130.293 | -0.9772 |
| 3 | 504.886 | 576.547 | 71.661 | 508.143 | 472.313 | -35.831 |
| 4 | 625.407 | 644.951 | 19.544 | 605.863 | 612.378 | 0.6515 |
| 5 | 511.401 | 530.945 | 19.544 | 488.599 | 504.886 | 16.287 |
| 6 | 509.804 | 517.915 | 0.8111 | 444.444 | 428.105 | -16.340 |
| 7 | 23.179 | 59.603 | 36.424 | 43.046 | 36.424 | -0.6623 |
| 8 | 258.278 | 268.212 | 0.9934 | 278.146 | 288.079 | 0.9934 |
| 9 | 387.417 | 394.040 | 0.6623 | 493.377 | 493.377 | 0.0000 |
| 10 | 430.464 | 390.728 | -39.735 | 417.219 | 337.748 | -79.470 |
| 11 | 513.245 | 523.179 | 0.9934 | 380.795 | 480.132 | 99.338 |

**Relationship with behavioral measure**

We then checked whether memory performance, as assessed by the discrimination index d', was related to the increase in proportions of scans linked to the task. A positive correlation was observed in the memory condition and a negative correlation in the control condition, the difference between the two correlations being significant (p=0.04, non-parametric permutation test; Figure 49, Table 14). Moreover, the correlation tended to be significant in the memory condition (p=0.058) but not in the control condition (p=0.504). These results do not support a strong relationship between memory reactivation and later task performance, although reactivations are associated with a weak enhancement of later memory performance.

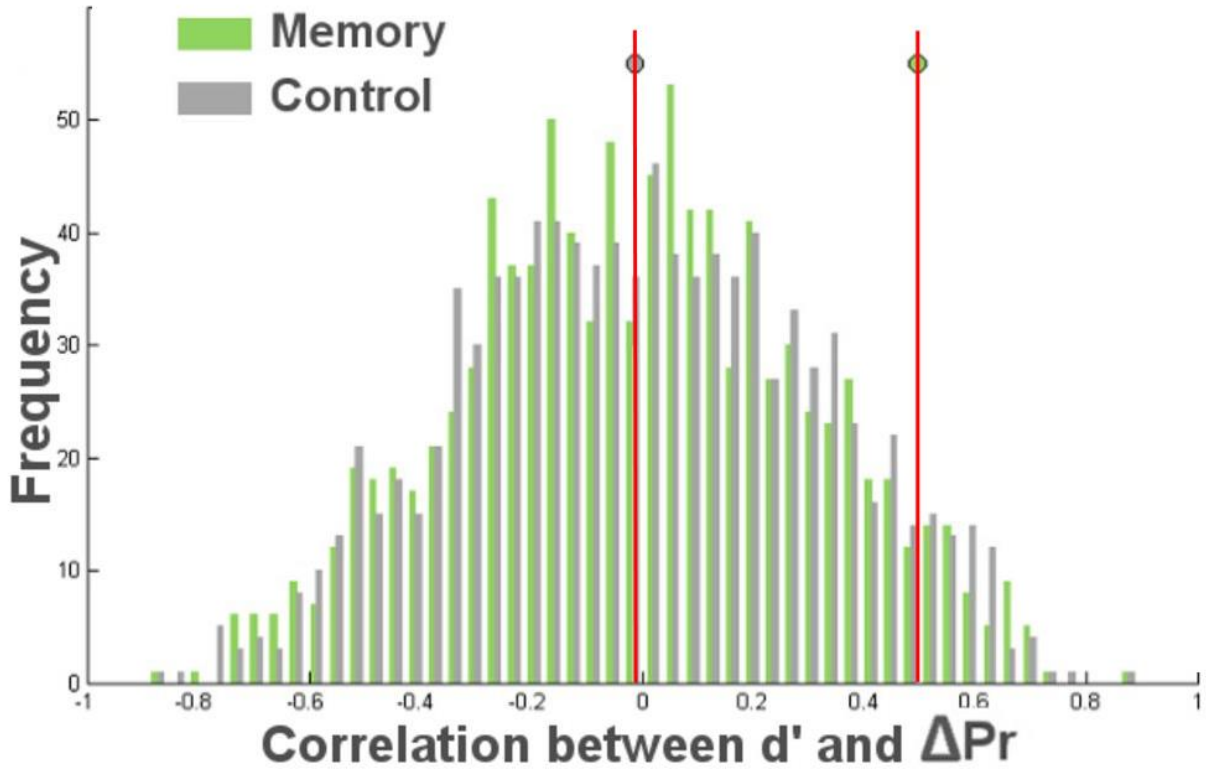


Figure 49. Null distribution obtained by permutations of correlation between ΔPr and behavioral performance (d') in memory (green) and control (gray) conditions. The actual correlations are displayed as circles for the memory and control tasks.

**Temporal evolution**

We also assessed the duration of reactivations. A larger proportion of episodes were observed for durations of at

least 4 scans in the post-task rest session, as compared to other rest sessions (Wilcoxon signed rank test, Figure 50a and b, Table 16). In addition, on average, the episodes were longer during the post-learning session than during any of the other sessions (Table 16), with significantly more episodes lasting 2 scans or more ($p=0.0493$, Wilcoxon signed rank test) and 3 scans or more ($p=0.0293$, Wilcoxon signed rank test; Figure 50c). This result suggests that after learning, scans significantly reinstating learned patterns are clustered into episodes lasting between 2 and 3 scans on average, i.e. 4 to 6 seconds.

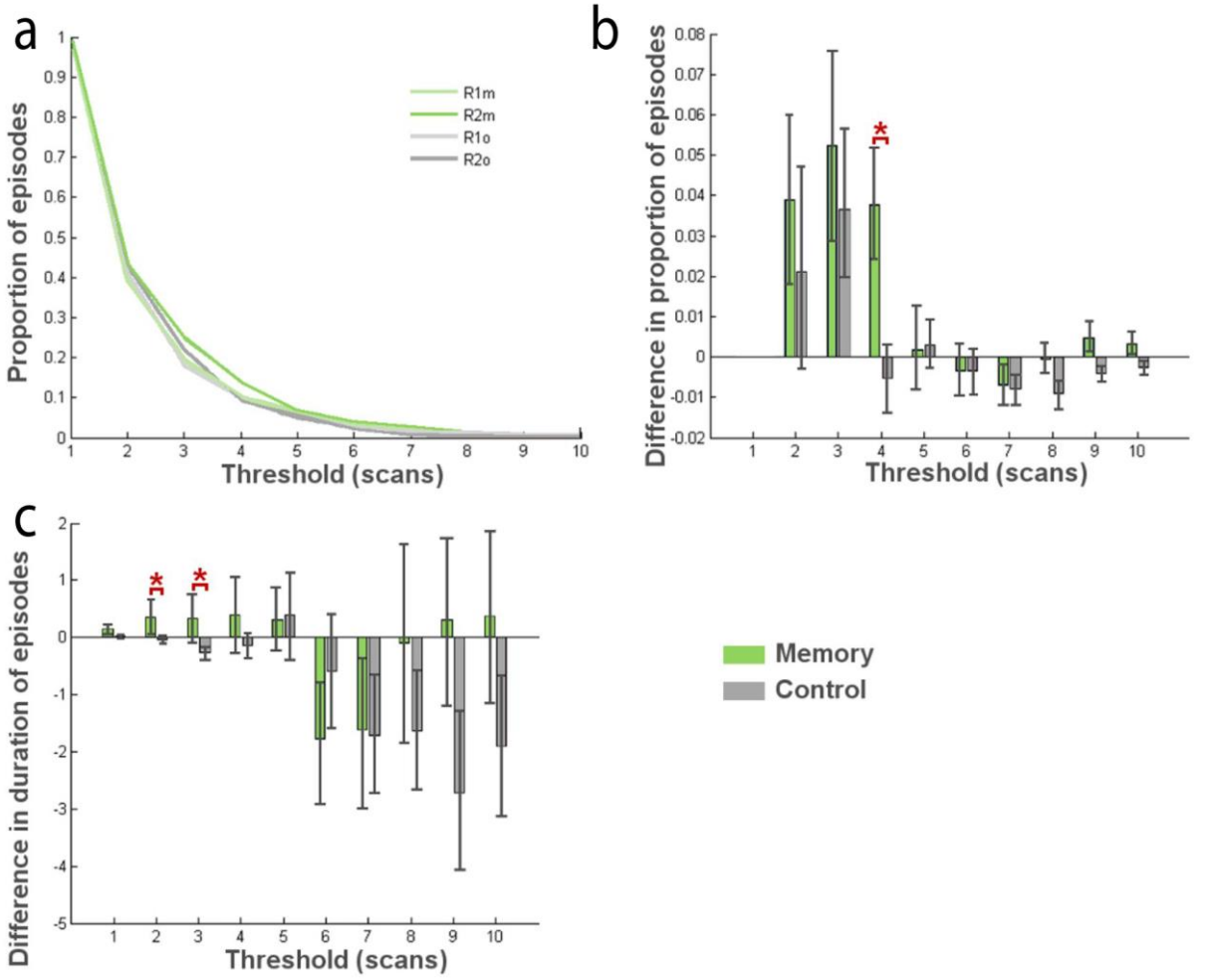


Figure 50. a. Average proportions of episodes lasting at least as long as the threshold (1 to 10 scans). b. Differences in proportions of episodes of scans, between pre-task and post-task ($p<0.05$ for episodes lasting at least 4 scans). c. Increase in episode duration between pre-task and post-task rest session is significant for episodes lasting 2 to 4 scans ($p<0.05$ for episodes lasting at least 2 or 3 scans). Averages over subjects, with normalized standard deviation. The memory and control condition are displayed in green and gray, respectively. Significant differences between conditions $p<0.05$ are marked with red asterisks.

Table 16. Proportions (pr) and average duration (dur) of episodes with a minimal duration varied from 1 to 10 scans, for each rest session. Some subjects did not show long episodes, and were counted as duration = 0 in the averages, resulting in underestimation of long episode durations (from about 6 scans).

| Minimal | R1m | | R2m | | R1o | | R2o | |
|---|---|---|---|---|---|---|---|---|
| duration | pr | dur | pr | dur | pr | dur | pr | dur |
| 1 | 1.0000 | 1.8367 | 1.0000 | 1.9829 | 1.0000 | 1.8046 | 1.0000 | 1.8296 |
| 2 | 0.3926 | 2.7888 | 0.4315 | 3.1441 | 0.4080 | 2.8158 | 0.4292 | 2.7849 |
| 3 | 0.1961 | 3.7584 | 0.2485 | 4.0847 | 0.1806 | 3.6124 | 0.2171 | 3.3593 |
| 4 | 0.1007 | 4.5361 | 0.1385 | 4.9259 | 0.0973 | 4.1431 | 0.0919 | 4.0019 |
| 5 | 0.0645 | 5.0664 | 0.0665 | 5.3833 | 0.0500 | 4.0978 | 0.0531 | 4.4978 |
| 6 | 0.0366 | 5.8227 | 0.0330 | 4.0515 | 0.0255 | 4.1591 | 0.0219 | 3.5606 |
| 7 | 0.0237 | 5.1061 | 0.0166 | 3.4924 | 0.0154 | 4.5909 | 0.0076 | 2.8788 |
| 8 | 0.0103 | 4.1364 | 0.0097 | 4.0455 | 0.0129 | 4.0000 | 0.0038 | 2.3636 |
| 9 | 0.0037 | 3.0000 | 0.0084 | 3.3182 | 0.0065 | 4.3636 | 0.0024 | 1.6364 |
| 10 | 0.0037 | 3.0000 | 0.0070 | 3.3636 | 0.0026 | 1.9091 | 0.0000 | 0.0000 |

**Phase information**

Finally, we estimated whether the phase structure implemented in the experimental design influenced the temporal organization of the reactivations during post-learning resting wakefulness through the estimation of transitions according to the forward and reverse cycles. Our results show that the proportions of transitions according to the forward cycle increase from pre-task to post-task rest sessions in the memory condition but decrease in the oddball condition ($p<0.05$, Wilcoxon ranked sum test; Figure 51).

Within the memory condition, the increase in proportions of forward transitions was not large enough to induce a significant difference between forward and reverse cycles (Figure 51). Regarding the reverse cycle, the memory and control conditions were not significantly different.

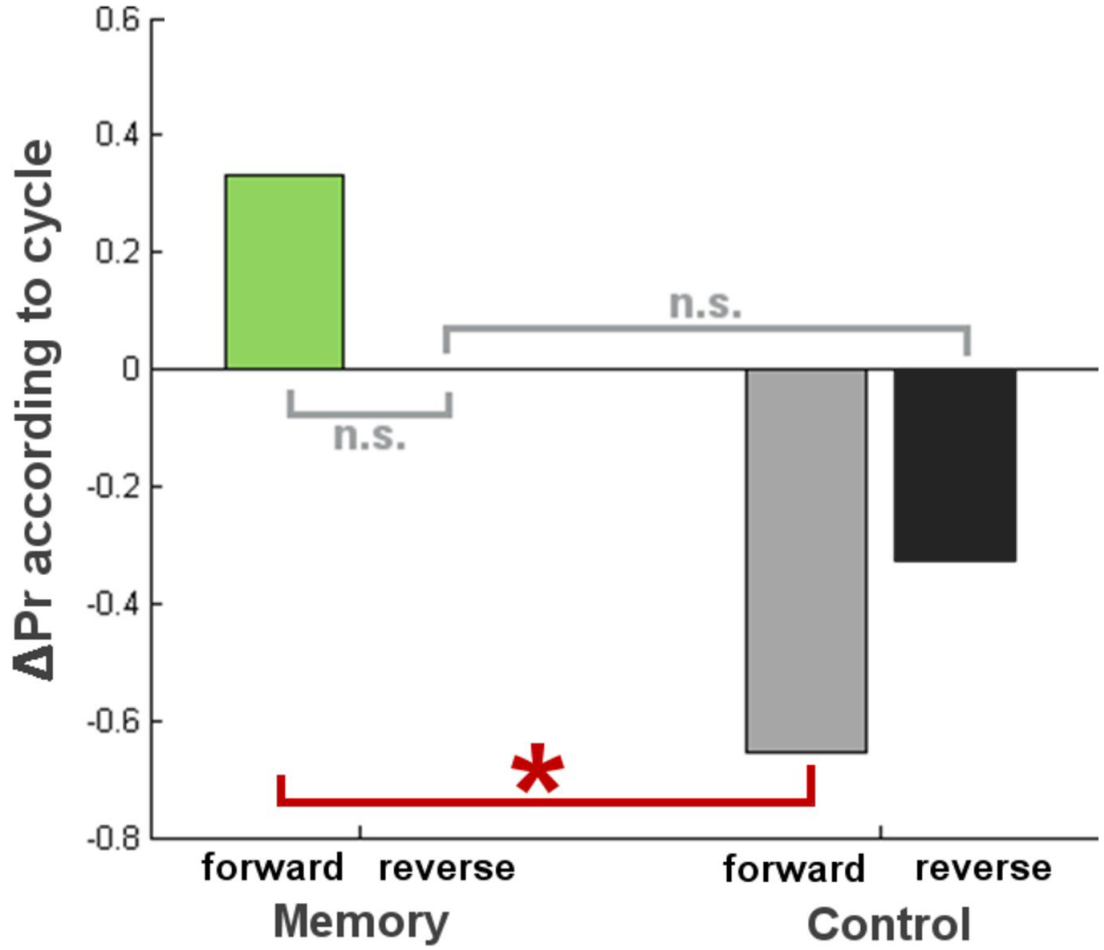


Figure 51. Phase information: post-learning modifications of forward and backward sequences. Increases in proportions according to the defined sequences: Pr(m) according to the forward (green) and reverse (not visible, =0) cycles and Pr(o) according to the forward (gray) and reverse (black) cycles.

**Effect of the significance threshold**

The effect of the threshold is represented in Figure 52, for the increases in Pr (Figure 52a) and for the p-value associated to the correlation between the increases in Pr (ΔPr, Figure 52b) for each condition and memory performance. Although the p-value threshold clearly affects the increases in Pr, ΔPr(m) is always larger than ΔPr(o). Furthermore, the p-values assigned to the correlations between the increase in Pr and the participants' behavioral performance seem to stabilize around the reported values for $0.05 < p < 0.1$.

Therefore, although the threshold affects the results, the results still hold when varying the threshold from 0.05 to 0.1. Moreover, while local minima and maxima can be

spotted on both graphs, our choice of $p < 0.05$ does not correspond to any extreme local variation of the computed measures and thus seems appropriate.

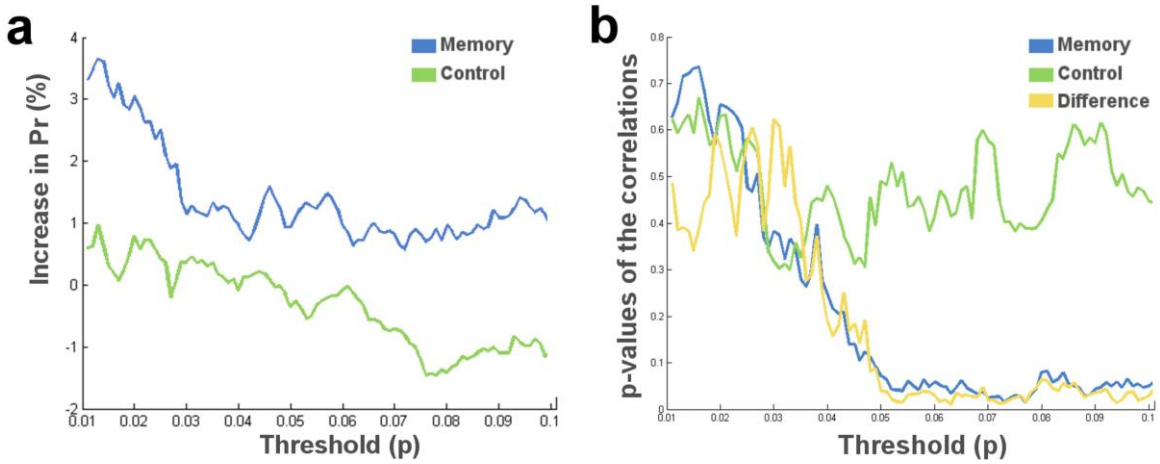


Figure 52. Effect of the p-value threshold. a. ΔPr from the pre-task to the post-task rest session (in %) for both conditions when varying the p-value threshold assessing a scan as significantly linked to the task from 0.01 to 0.1. b. P-values of the correlations rho between ΔPr and d' for both the memory (blue) and control (green) conditions, as well as the p-value of their difference (yellow).

## 4.4. Discussion

In this study, we characterized the spontaneous brain activity related to a fresh memory trace in healthy human volunteers during resting state wakefulness. To this end, we relied on a rigorous within-subject cross-over experimental design with balanced and controlled conditions. fMRI time series were collected during rest sessions flanking both a memory and control task session, and a follow-up memory retrieval session using an innovative approach: memory processing was not evoked by cues but occurred spontaneously.

This complex dataset presented challenges that could not successfully be solved using standard techniques such as univariate models. In order to overcome these issues, we applied four different state-of-the-art techniques (dynamic causal modeling, explained variance, identification of spatial networks and multivoxel pattern analysis) which gave variable results. The pattern analysis, which allowed modeling of spontaneous brain activity without suppression of the temporal evolution and spatial aspects, is

based on an innovative machine learning approach: the classifier was trained on brain activity during memory retrieval rather than encoding, we used a confidence metric to assess replay events during resting state, and we investigated the temporal evolution of significant reactivations related to the temporal course of the learned task (encoding).

**Summary of main findings**

We found that 1.11% more scans were task-related after task learning than before. In addition, the difference in proportion of resting scans linked to the memory task between pre- and post-task sessions tended to predict later memory performance, suggesting that the post-task spontaneous brain activity patterns were related to memory processing. By contrast, the proportion of scans related to the memory session after a control task was 0.26% lower than before the control task, suggesting that this task had a repressive effect on activity patterns related to the memory session. The proportion of scans containing task-related brain activity was non-null for all subjects during all rest sessions, even before task learning, implying that spontaneous activity in the ventral visual stream is an omnipresent phenomenon.

Our results extend the understanding of human spontaneous brain activity and its relationship to early memory processing. They add to the growing body of evidence showing that human memory processing can indeed be investigated with fMRI, is not exclusively linked to sleep but occurs during resting state as well, and is related to behavioral measures of memory performance.

**Spontaneous on-going activity in higher order brain areas**

A first important finding was that activity patterns spontaneously emerge in unimodal associative areas of the visual ventral stream during resting wakefulness, in the absence of any visual stimuli, even before any experimental treatment (i.e. during pre-task rest sessions). These activity patterns correspond to those elicited by complex visual

stimuli such as faces, buildings or animals during the functional localizer and task encoding sessions.

This finding extends previous results recorded in animals showing spontaneous reinstatement of visual patterns in primary visual cortex (Arieli et al, 1996; Tsodyks et al, 1999; Kenet et al, 2003) and indicates that spontaneous brain activity patterns also occur in higher order areas of the ventral visual stream (fusiform face area, parahippocampal place area, and an animal-specific region). This result is in agreement with a previous study which demonstrated an enhanced functional connectivity between the hippocampus and a portion of the lateral occipital complex during post-task resting wakefulness (Tambini et al, 2010), although we could only find hippocampal activation during post-task rest in one volunteer. On the contrary, we could confirm large activations in the parahippocampal gyrus and perirhinal cortex in most participants (Staresina et al, 2013). We also found stable and firm evidence supporting previous memory consolidation studies in humans (Deuker et al, 2013; Staresina et al, 2013; Tambini and Davachi, 2013).

**Memory offline processing can be detected during wakeful resting state using fMRI**

The second contribution of the current experiment consisted of characterizing the genuine neural correlates of a fresh memory without altering it by retrieval processes but solely by decoding spontaneous brain activity in the ventral visual stream during post-task resting state wakefulness. Our results confirm that offline processing of explicit memories can indeed be investigated during resting state wakefulness in healthy human volunteers with fMRI, a macroscopic, non-invasive neuroimaging technique, by establishing a rigorous state-of-the-art methodology based on multivoxel pattern analysis.

Moreover, the density of visual activity patterns during post-task rest session, but not during the rest session after the auditory task, tended to predict later memory performance. This result suggests to the very least that the repetition in post-learning spontaneous activity related to recent memories participates in their maintenance.

**Methodological strengths**

Third, the current design is based on a randomized within-subject crossover design which accounts for two main confounding factors, order effect and task-selectivity. These factors are seldom taken into account in the literature (Hassabis et al, 2009; Chadwick et al, 2010; Kuhl et al, 2012a; Kuhl et al, 2013) while some studies are not immune to confounds such as concurrent practice or rehearsal (Kuhl et al, 2013; Jafarpour et al, 2014).

This methodological aspect is of critical importance when trying to decipher spontaneous brain activity. Indeed, it is known that resting state brain activity can spontaneously express activation patterns similar to those observed during processing of external stimuli (Tambini et al, 2010; Deuker et al, 2013; Tambini and Davachi, 2013). Accordingly, we observed a significant spontaneous activity in both the memory and control tasks. However, the changes in the rate at which activation patterns specific to the memory task are re-expressed after the memory task strongly suggests that they reflect further processing of the encoded information.

Our analysis consisted of training of the classifier on the retrieval session (instead of the encoding session) because this was the condition closest to the potential spontaneous replay during resting state: 1) cognitive processes during memory retrieval are less constrained than during the completely controlled encoding session; 2) duration of the retrieval session was subject-dependent which increases variance of the fMRI signal; and 3) during retrieval, the memories are activated in the absence of any visual input.

Moreover, we used a large number of controls at both the design (the order of the memory and control condition being randomized across participants) and methodology (a confidence metric to assess replay events during resting state, as no ground truth exists in this condition).

One of the methodological strengths is that we extensively explored the optimal classification method. We did this because excellent classifier accuracy was an important prerequisite in our study. Our preparatory study showed

that for complex, unbalanced time series containing self-generated mental states, best accuracies are obtained by a feature selection combining a specific GLM and a recursive feature addition, in terms of balanced accuracy, and classification by binary one-versus-one Gaussian processes (Schrouff* et al, 2012). We found that GP seems more appropriate for markedly unbalanced data sets than SVM and is thus preferable for a realistic experimental setup, as in our study. This preparatory step moves beyond previous studies which used a one-way ANOVA for feature selection and a standard linear support vector machine for classification (Deuker et al, 2013). Moreover, we estimated the chance level through a permutation procedure, meaning that the chance level varied across participants.

Due to this rigorous experimental design, the interpretation of our results is also immune from non-specific effects. For instance, the increased duration of the repeated activity after the memory task cannot be simply accounted for by the autocorrelation of the fMRI signal. Indeed, if this were the case, the same effect should be observed with the control oddball task and it is not.

In addition to the rigorous experimental design, our results were derived from state-of-the-art modeling strategies and were strictly controlled for false positives and multiple comparisons. These modeling procedures first involved the automatic selection of a spatial pattern, i.e. the 1000 most informative voxels, through a two-step feature selection technique (Schrouff* et al, 2012). This is an asset compared to an observer-dependent selection of regions of interest (Tambini et al, 2010; Staresina et al, 2013) because 1) it allows for variability across subjects; 2) it is not biased by observer interventions; and 3) previous work indicated that information in other areas was nonetheless associated with highly reliable classifier-based evidence for category representation (Haynes and Rees, 2006). Such bias might emphasize the role of the entorhinal cortex and the retrosplenial cortex in offline memory processing (Staresina et al, 2013) while visual sensory areas (e.g. FFA, PPA, hippocampal place cells) might be neglected despite their implication in memory offline processing in animal (Ji and

Wilson, 2007) and in human experiments (Tambini et al, 2010).

One of the major concerns with pattern classification is that classifiers might be overfitted to the dataset. We reduced this risk by limiting the feature space to the 1000 most active voxels, by using the optimal classifier for our dataset (Schrouff* et al, 2012), and by the good classification performance in all sessions. Namely, overfitting would have substantially reduced classification accuracy.

Furthermore, care was taken to perform feature selection without using the category-specific information outside a nested cross-validation. This is a common flaw in various machine-learning based analyses, and can take multiple forms such as subtracting category-specific averages of the signal (Jafarpour et al, 2014) or selecting features based on T- or F-tests performed on the whole data set (Deuker et al, 2013). In our work, we therefore present unbiased data-driven feature selection.

Another challenging aspect of the present work is the classification of resting periods, in which a ground truth is not available. Previous works have performed similar analyses (Deuker et al, 2013; Horikawa et al, 2013; Staresina et al, 2013). However, they usually assumed that the predictions obtained for each time point were true, although it is highly unlikely that brain activity is permanently linked to the limited set of classes of the encoding/recall task. In our work, we present a novel approach, based on the confidence of the classifier, to assess whether one time point is *significantly* linked to the memory task or not. Furthermore, significance was assessed in a conservative way, first by considering 1000 permutations of the labels to obtain the null distribution of the confidence measure, and second by correcting this distribution for multiple comparisons (i.e. multiple time points). Therefore, it is important to note that, although the results presented in this work might seem less strong than in other related studies, they were obtained using a stricter methodology and conservative significance assessment.

**Temporal organization of spontaneous brain activity is different during reactivations**

Our fourth main finding is that learning a spatiotemporal array of complex pictures significantly alters the temporal organization of spontaneous brain activity. During a resting session following encoding, task-related activity patterns are clustered in episodes of longer duration (4 to 6 seconds) and tend to follow the phase structure imposed by the memory task. This result echoes the preservation of temporal patterning of neural ensembles within and between cortical regions observed during post training wakefulness in monkeys (Hoffman and McNaughton, 2002).

This suggests either a reactivation of on average two images of our task, or a temporal compression of more reactivated images. Indeed, previous studies found that the time frame of the repeated patterns is scaled in sleep (Louie and Wilson, 2001; Lee and Wilson, 2002; Euston et al, 2007; Ji and Wilson, 2007). However, in our study it was not possible to derive the true number of rehearsed images and therefore we cannot draw a conclusion about a possible scaling factor.

Task-related activity patterns during post-learning resting state tend to follow the same phase structure imposed by the memory task. Unexpectedly, however, multivoxel pattern analysis revealed that the increased phase structure was a nonsignificant trend in the memory condition and was mainly driven by a rather puzzling decreased phase structure in the control condition. Although only a trend, this result echoes the preservation of temporal patterning of neural ensembles within and between cortical regions observed during post training wakefulness in monkeys (Hoffman and McNaughton, 2002).

The functional importance of the maintained temporal organization of regional brain activity can be variably appreciated. To some, it may seem trivial that neural populations recruited following a given order during encoding would continue to do so afterwards. By contrast, others may consider that the very maintenance of this temporal information is central to the memory that has just

been generated. The repressive effect of the control task remains currently unclear.

Although we did not test other durations than the 10 minute rest sessions immediately following task learning, our results confirm that spontaneous reactivations in humans occur within a short timeframe after task learning. A decrease across time of the proportion of scans linked to the task in the post-task rest session for the memory condition could not be found. This is in agreement with others who found no effect of time on seed correlations in a 10 minute rest period either (Tambini et al, 2010), although animal studies using rest longer periods found a decrease of the strength of correlations (Wilson and McNaughton, 1994; Kudrimoti et al, 1999). Our result indicates that enhanced correlations in the post-task rest were generally consistent and present throughout the entire rest scan. Another possibility is that a period of only 10 minutes is too small to detect a significant effect of time.

As (Tambini and Davachi, 2013) already suggested, it will be critical for future studies to determine whether these findings relate to extended measures of long-term memory, and examine how long these neural measures of persistence are detectable, incorporating longer rest periods, as in (Harmelech et al, 2013).

**Anatomical connections in the ventral visual stream need to be untangled**

At the microscopic network level, the temporal order following which two connected neurons are activated is an important aspect of synaptic plasticity (Bi and Poo, 1999). We report here that the temporal order of brain activity on a larger scale, measured by the amount of transitions between categories, tends to be maintained after task learning, but tends to be reversed after a control task. These results suggest that the increase in proportion of scans reinstating learned activity patterns is organized according to the forward cycle, i.e. transitions imposed by the structure of learned material, a situation reminiscent of time-dependent synaptic plasticity.

The current results are not consistent with the reverse sequential replay reported in the rat hippocampus during awake periods following spatial experience (Foster and Wilson, 2006). However, beyond the difference in the level of description (activity of neurons versus activity patterns of brain areas), the present experimental conditions considerably differ from those reported in rodents. To the least, the current results suggest that reverse order replay may be considered neither selectively related to resting wakefulness, nor a general mechanism of learning and memory in mammals.

Another concern was the model selection of the dynamic causal modeling analysis. Model selection of the forward and backward models was based on previous experiments (Louie and Wilson, 2001; Foster and Wilson, 2006). However, we could not exclude the fully connected model because anatomical connections are not yet described for this brain region. Bayesian model selection consistently revealed greater evidence in favor of the fully connected model, more than the forward or backward families, in all rest sessions, and no correlations with behavioral performance could be found at all. However, the lack of evidence in favor of the forward or backward connections does not reflect the complete absence of information flow in this direction, but rather implies a bidirectional modulatory influence. Our results do not exclude the forward or backward models per se but suggest that these connections play a minor role in the observed hemodynamic response during viewing of faces, buildings and animals.

It can be argued that baseline spontaneous brain activity always moves in the forward order, or that the ventral visual pathway from the primary visual cortex to higher order areas, the limbic system and the prefrontal cortex, travels in this direction (Fairhall and Ishai, 2007). Previous studies found a stronger anatomical input from the parahippocampal to the perirhinal cortex than vice versa (Suzuki and Amaral, 1994). Indeed, category specific effects in the occipitotemporal cortex can be mediated by bottom-up mechanisms, by inputs from early visual cortex (Mechelli et al, 2003).

**Connectivity at the regional and network level needs to be unraveled**

To address this question, we employed independent component analysis in order to investigate the connectivity within and between regions. Our results confirm previous research that the attention networks (ventral and dorsal) were the most affected by the tasks (Smith et al, 2009). However, increases in integration between the hippocampal and maze networks were also expected, or between the hippocampal and visual networks in the memory condition, and this was not the case. This is not in agreement with (Tambini et al, 2010), who found an enhanced functional connectivity between the hippocampus and a portion of the lateral occipital complex during rest following a task with high subsequent memory compared to pre-task baseline resting connectivity. Furthermore, they found that this enhance in connectivity was not present during rest following a control task with poor subsequent memory.

According to (Smith et al, 2009), the connectivity of the default mode network should not be affected by a task. Therefore, some of our results were unexpected, such as the significant increases in integration between the default mode and ventral attention networks, and between the default mode and hippocampal networks for the memory condition.

**Spontaneous activity can be repressed by an unrelated task**

Our fifth interesting finding was that spontaneous brain activity during resting state wakefulness can be also be negatively modulated by prior cognitive tasks. Unexpectedly, the visual memory task using relevant stimuli did not significantly modify the abundance of spontaneous visual activity as compared to before learning, whereas the unrelated control task (an auditory attention task) considerably reduced this spontaneous activity, during at least 10 minutes. These results provide an objective evidence that unrelated cognitive tasks may interfere with early memory processing, a situation reminiscent of the interactions observed between

procedural and explicit memory consolidation (Brown and Robertson, 2007). Although previous research showed that concurrent competing retrieval of other memories impairs retrieval of newer memories (Kuhl et al, 2012a), the functional significance of these transmodal modulations is currently unclear.

An alternative explanation could be that the temporal resolution of fMRI would be not sufficient to detect transient spontaneous reactivations. Further studies using techniques such as electroencephalography or intracranial electrocorticography should further examine this possibility.

**Inter-subject variability**

A high inter-subject variability was an important limiting factor in our studies. In the interest of studying cerebral correlates of memory consolidation with objective neuroimaging methods, we concluded in the previous chapter that hypnagogic hallucinations were not an optimal study design because only a minority of all hypnagogic hallucinations was task-related and they were not consistently reported by every volunteer.

However, memory processing during resting state wakefulness instead of sleep onset turned out to be even less reliable across subjects. Indeed, the classifying model for brain activity was not consistent across volunteers. A further issue was the large variability in proportions of task-related scans during the pre-task rest session in the memory condition. These differences in cortical activation likely reflect subject-specific variations in signal-to-noise ratio rather than variations in functional architecture. First, volunteers might have used different learning strategies, which affected the sensitivity of the decoding technique and decreased our ability to model the corresponding rest sessions. Second, some volunteers have mentally rehearsed the images during the post-task rest session in the memory condition, as we found out during the debriefing afterwards. It is known that such memory retrieval recruits frontal regions (Nyberg et al, 1996) as well as medial temporal lobe structures (Kuhl et al, 2013) and distributed

patterns representing various features of the event (Johnson et al, 2009). This would elicit a higher level of noise in the dataset compared to our effect of interest, making it more difficult to classify correctly.

**Alertness**

Differences in drowsiness and alertness can have an important influence on mental processes (Tagliazucchi and Laufs, 2014), as we confirmed in our study of hypnagogic imagery. A recent study revealed a reliable loss of wakefulness in a third of all volunteers in resting state experiments within 3 minutes (Tagliazucchi and Laufs, 2014). However, this factor is unlikely to contribute to our resting state findings because precautions were taken that our volunteers maintained full wakefulness during the complete experiment. A break was included between both conditions, volunteers were instructed that it was critical to maintain wakefulness at all times, task order was counterbalanced across participants, and memory performance between both groups of participants did not differ. Besides, a study which combined fMRI with EEG to objectively quantify the amount of occipital alpha activity, found no difference in drowsiness-related EEG activity between memory and control tasks (Deuker et al, 2013). However, despite our precautions, we cannot 100% exclude the possibility that some volunteers drifted off to sleep stage one, because we did not objectively monitor the vigilance state with EEG.

**Baseline level**

When we computed the explained variance during resting state immediately following the memory task, approximately 0.50% of the BOLD signal in a category-specific region could be explained by the task, and on average 0.95% could be explained by the transition from one category to another. Unexpectedly, these percentages were not significantly different from the other rest sessions. We hence could not confirm previous animal studies which found an explained variance of 5% during pre-task sleep that augmented to 10% à 15% during post-task sleep

(Kudrimoti et al, 1999; Hoffman and McNaughton, 2002; Pennartz et al, 2004).

It can be argued that the baseline level of "random" brain activity is not 5% but much lower. A logical question would be whether the explained variance after and before the memory task were different (which was not the case for our study). However, a more correct question would be whether the EV after the memory task was different from zero, as this measure already takes into account the activity before the task. We found that this was indeed the case. Unexpectedly, no difference could be found between the memory and control condition.

**Hippocampal replay?**

Hippocampal replay is hypothesized to contribute to memory consolidation (Buzsaki, 1989; Sutherland and McNaughton, 2000; Rasch and Born, 2007). In line with this prediction, previous work in rodents has shown that multivariate patterns of hippocampal activity are reactivated in sleep (Wilson and McNaughton, 1994; Nadasdy et al, 1999; Lee and Wilson, 2002) and awake periods (Davidson et al, 2009; Karlsson and Frank, 2009). The extent of hippocampal reactivation in rodents has been related to spatial memory improvements (Dupret et al, 2010). Prior work in humans using fMRI has shown that resting connectivity between the hippocampus and encoding-related cortical areas can be modulated by an associative encoding experience (Tambini et al, 2010; van Kesteren et al, 2010; Tambini and Davachi, 2013) and that these experience-related changes are correlated with later memory (Groen et al, 2011). In the present study, we did not focus on hippocampal activity but this may be an interesting path to explore.

It can be questioned whether we are examining memory consolidation per se, immediately following the task during resting state. First, importantly, our data suggest that conscious retrieval of the learned material during post-task rest does not account for the activity patterns detected by our decoding scheme, suggesting that these activity patterns are truly spontaneous. Second, we discarded

volunteers that consciously rehearsed the task the whole time, despite the experimental instructions. The included volunteers rehearsed only a few images, sometimes voluntarily, but sometimes the images appeared spontaneously in their mind. Even with these precautions, we cannot completely exclude the possibility that we detected rather memory retrieval than offline consolidation.

## 4.5. Conclusion and perspectives

Present data, analyzed with multivoxel pattern analysis, show that initial maintenance of human episodic memories involves the spontaneous reinstatement of regional activity patterns which respects the temporal structure of the learned material. However, the high inter-subject variability and the absence of results from our other analyses (dynamic causal modeling, explained variance and identification of spatial networks) suggest that this effect is small and that fMRI may not be the most suitable technique to detect and characterize directly a fresh memory trace. The detailed temporal dynamics of the coupling between the three investigated category-specific regions could not be examined with fMRI. Moreover, the scaling factor of mnemonic traces was not possible to investigate due to the limited temporal resolution of the hemodynamic response.

High density electroencephalography and electrocorticography, which have an excellent temporal resolution, could provide more insight in this problem and might be more appropriate for future investigations. However, the classification of such datasets would present a new challenge due to the low signal-to-noise ratio.

# 5. CONCLUSION & PERSPECTIVES

Memory processing can be described as brain activity which adapts to the environment in order to update information. Such subtle changes in brain activity and connections are difficult to detect with non-invasive macroscopic neuroimaging methods in healthy humans. We have tested two different designs to probe the maintenance of recent memories in spontaneous brain activity (sleep onset and resting state) using multimodal techniques (behavioral, EEG and fMRI). Although our two experiments were quite different with respect to experimental setup, dependent variables and implied memory systems, in this last chapter we list some of the main findings, advances and limitations of both studies and some future perspectives.

**Summary of main findings**

Our first sleep onset EEG experiment gave encouraging results:

- We were able to show the incorporation of task-related mental content into hypnagogic hallucinations during daytime sleep, conform to other studies of hypnagogic imagery during nighttime sleep (Stickgold et al, 2000; Emberger, 2001; Stickgold et al, 2001a; Wamsley et al, 2010).
- We could confirm with standardized recording techniques that these hypnagogic hallucinations occur only during sleep stage one and the beginning of stage two.

Nevertheless, this behavioral sleep onset experiment did not appear as a useful paradigm due to the low proportion of recall and the difficulties inherent to the condition, such as multiple awakenings per subject and memory loss.

For our second experiment using fMRI, we developed a rigorous design that allows for testing memory maintenance during resting state wakefulness, which takes into account order- and task-specific effects. These fMRI data were analyzed with multivariate decoding techniques and also led to some promising findings:

- We were able to demonstrate spontaneous activation of stimulus-related activity patterns, even before training, and in both the memory and control condition. An important detail is that this is the case even when the volunteers were not instructed to mentally retrieve the task.
- We showed a change in the temporal organization of reactivation.

**Limitations and improvements of our studies**

A first limitation of the resting state study was that we could not confirm the findings of the multivariate pattern analysis with other techniques, which underlines the importance of using a robust and very strict multivariate analysis. A second important restraint was that we were not able to robustly show a replay during post-learning resting state. Instead, we showed that an unrelated task repressed the spontaneous task-related brain activity. Based on the animal literature and recent human EEG and fMRI experiments (Tambini et al, 2010; Deuker et al, 2013; Staresina et al, 2013; Tambini and Davachi, 2013) which definitely show evidence for offline memory replay, we surmise this is essentially due to the limited temporal resolution of the fMRI BOLD signal.

The main advantage of studying spontaneous replay is that it is unlikely to introduce any cue-related effects, e.g. through sensory stimulation. However, it also complicates the analysis because the signal-to-noise ratio is lower than voluntary brain activity. As we noticed, this might lead to some unexpected effects, especially in the very short task-adjacent resting periods.

EEG, ECoG and MEG might be more suitable techniques than fMRI to further investigate offline processing of explicit memories, although these techniques present new methodological challenges such as a poorer spatial resolution. Simultaneous fMRI and EEG would be another option if the technical limitations can be tackled, such as the degradation of the signal and image quality due to the interference between both recording techniques (Huster et al, 2012) and the low signal-to-noise ratio of the EEG signal (Gutierrez and Escalona-Vargas, 2010).

In line with previous work, we found that the strongest encoding patterns (i.e. faces and animals) preferentially persisted into postlearning rest periods and could be classified with higher accuracy. This underlines the importance of a motivating, engaging task. A possible option to improve this would be the opportunity to earn a bonus money reward depending on the recall accuracy at testing (Kuhl et al, 2012a).

It would be interesting to further examine task-related hypnagogic hallucinations and their contribution to memory processing. The emergence of subliminal presentations in sleep-onset imagery would be a possible way to examine offline memory processing. Relevant for such experimental design, a recent study showed that subliminal presentation of acoustic cues that had previously been paired with image associations, improved later recall performance of these associations after sleep (Rudoy et al, 2009).

**Perspectives**

From a methodological point of view, decoding spontaneous brain activity is still a challenge and probably it will stay a challenge for the next decade(s). We attempted to tackle this by using a very strict task, robust analyzing methods, and by pushing the analysis to its limits. With the current scientific knowledge, we could not derive any more information from our fMRI dataset. Therefore we suggest that future research studies should continue with electrophysiological and more direct neurological measurements. In the far future, brain decoding might become a useful clinical tool to examine neurological and psychiatric disorders, for example intrusive thoughts of depressed patients, hallucinations of schizophrenics, and it might provide insight in therapies in neurology and psychology. In research, decoding of dream content might be an interesting path to explore.

Examining spontaneous brain activity, and especially decoding ongoing offline brain activity, is still a largely unexplored area. This makes it a very interesting and challenging domain to discover.

# 6. ANNEXES

## 6.1. Examples PSG recordings

**Arousal**

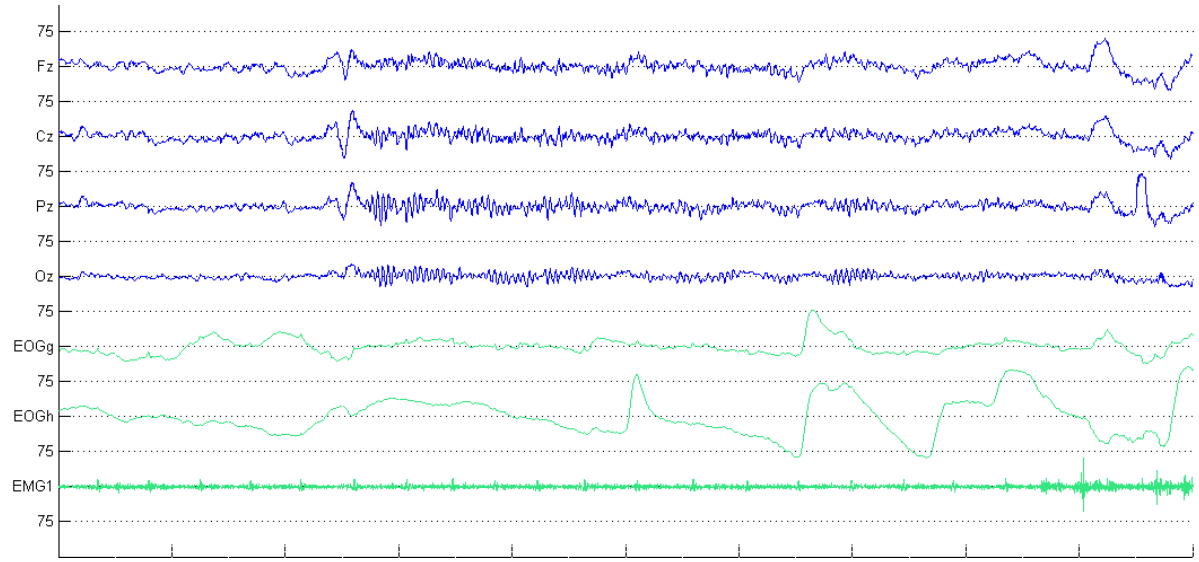


Figure 53. PSG showing an awakening by an auditory stimulus in sleep stage 1, which evoked a spike in the EEG, followed by alpha rhythm, saccades and muscle activity. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG measurements, and green chin EMG)

## Wakefulness

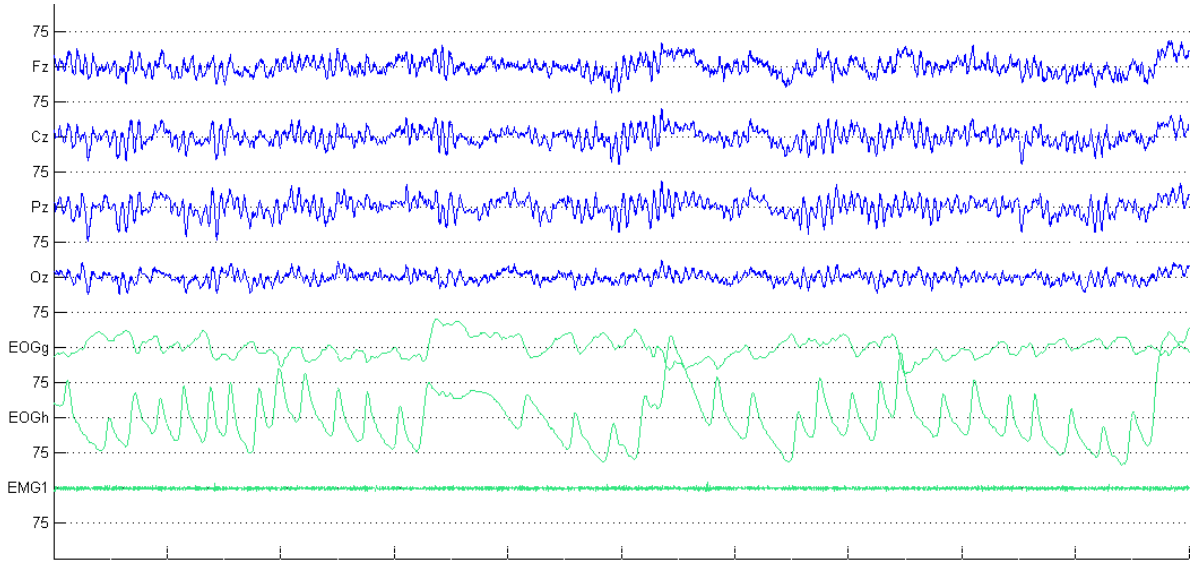


Figure 54. PSG during wakefulness. This figure shows nice alpha rhythm at Oz and fast horizontal eye movements, which are typical of the relaxed wake state with closed eyes. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

**Stage 1**

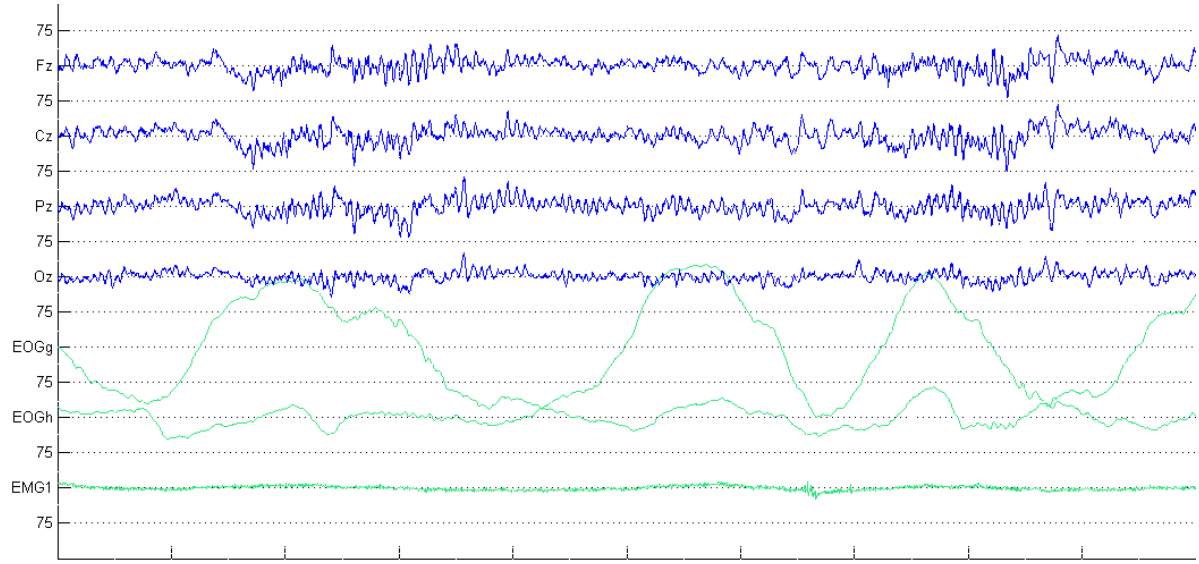


Figure 55. PSG during sleep stage 1, with slow horizontal rolling eye movements and fragmented alpha rhythm, which are the first indicators of sleep stage 1. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

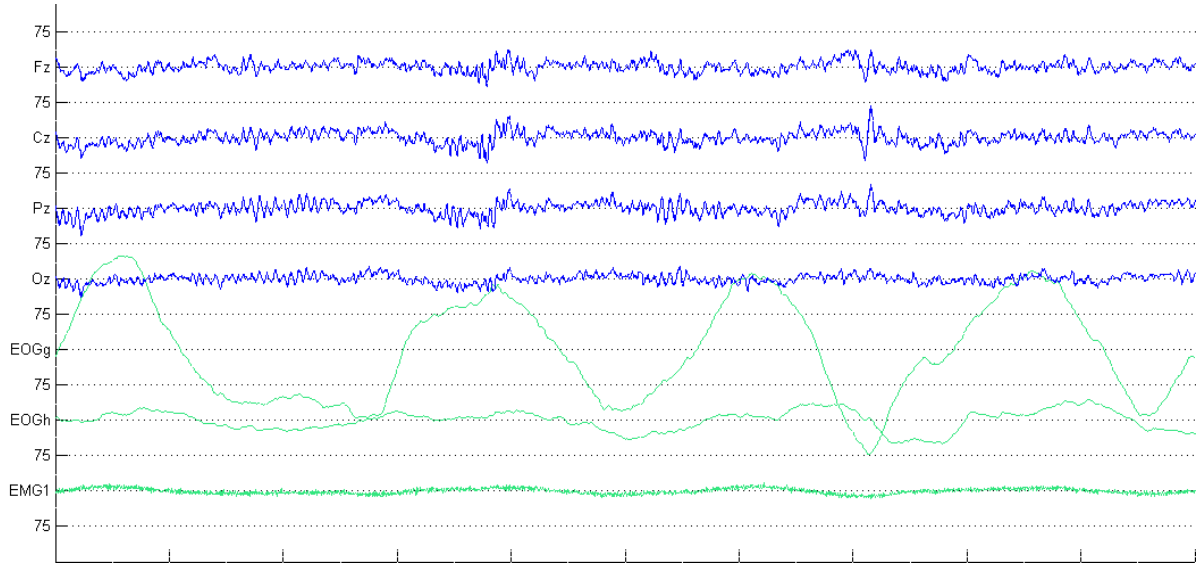


Figure 56. PSG during sleep stage 1, showing slow horizontal rolling eye movements, a progressive disappearance of alpha rhythm and appearance of theta rhythm and a central vertex sharp wave, which are the first indicators of sleep stage 1. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

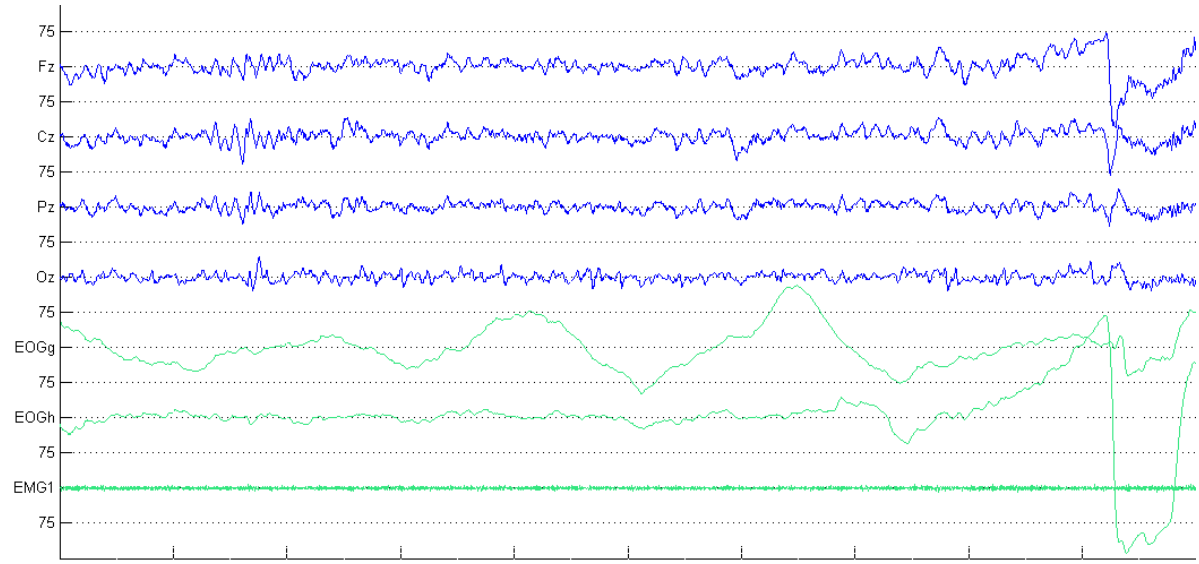


Figure 57. PSG during sleep stage 1, with slow horizontal rolling eye movements, a progressive disappearance of alpha rhythm, and appearance of theta rhythm. At the end of this 20 second epoch, the subject is awoken by an auditory stimulus, which immediately evokes a spike and a fast low voltage pattern in the EEG and fast eye movements. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

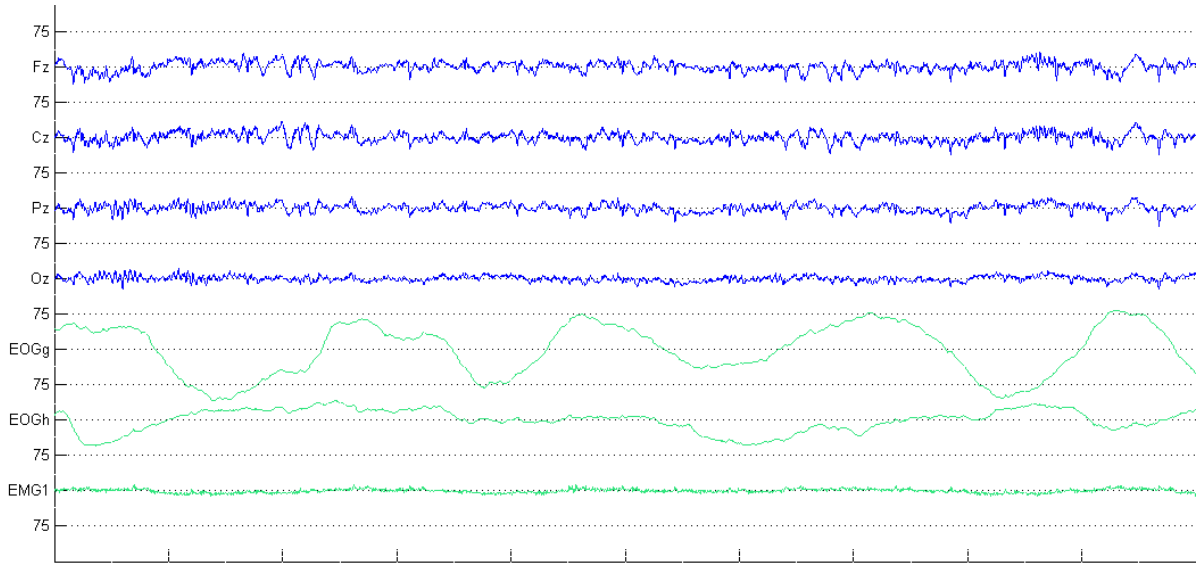


Figure 58. PSG during sleep stage 1, showing horizontal slow eye movements and a progressive disappearance of alpha rhythm. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

**Stage 2**

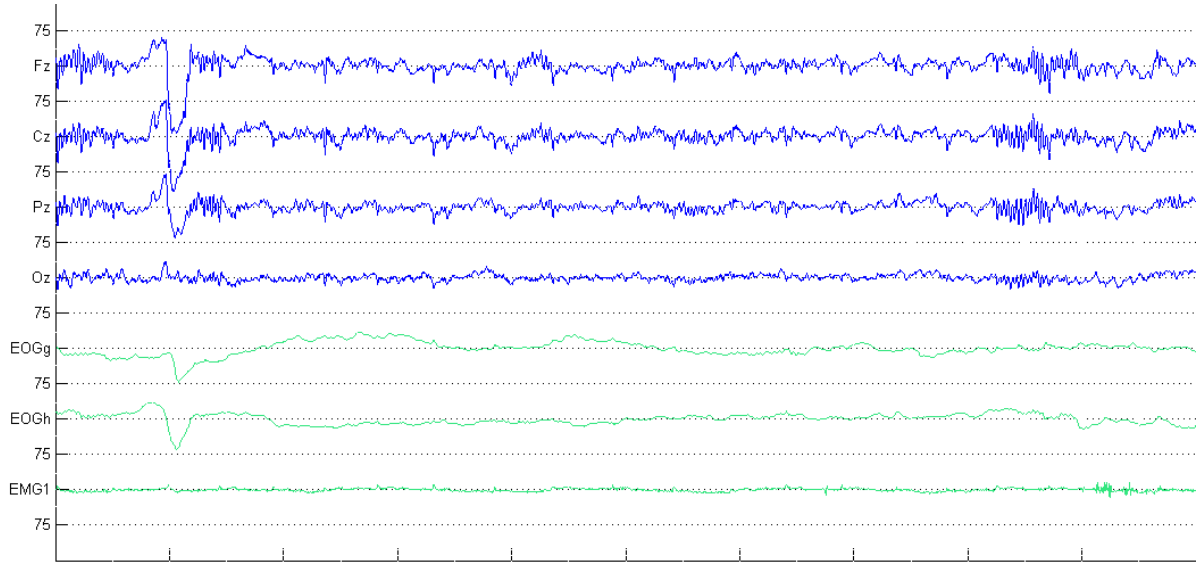


Figure 59. PSG during sleep stage 2, with several sleep spindles and a K-complex. Although there are no eye movements, an overshoot of the K-complex is visible in the EOG. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

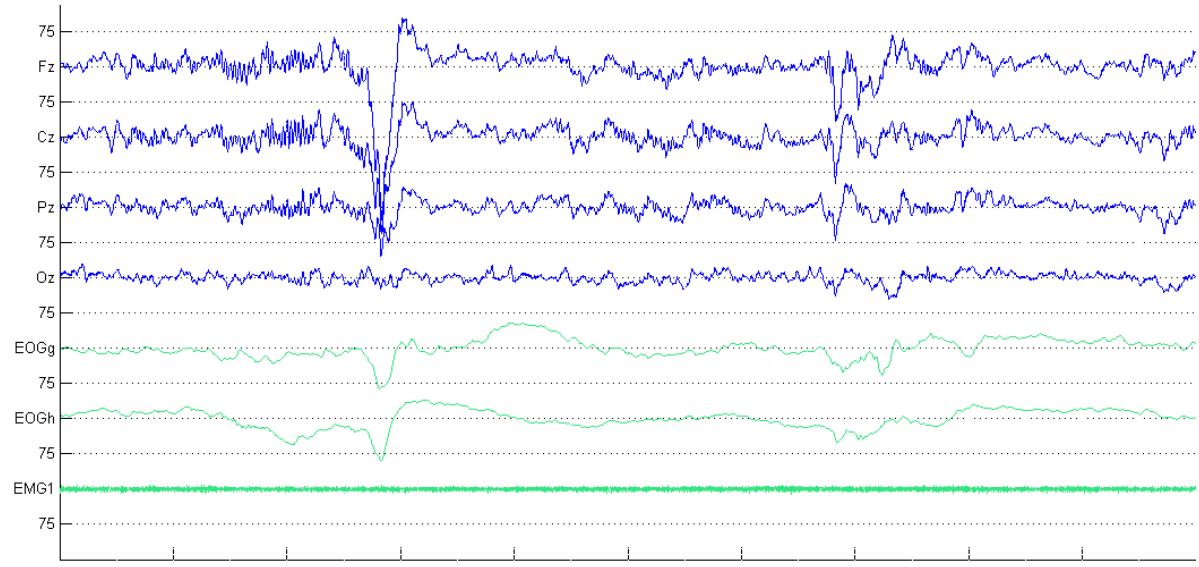


Figure 60. PSG during sleep stage 2, showing a sleep spindle and large amplitude K-complexes which overshoot to the EOG recordings. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

## SWS

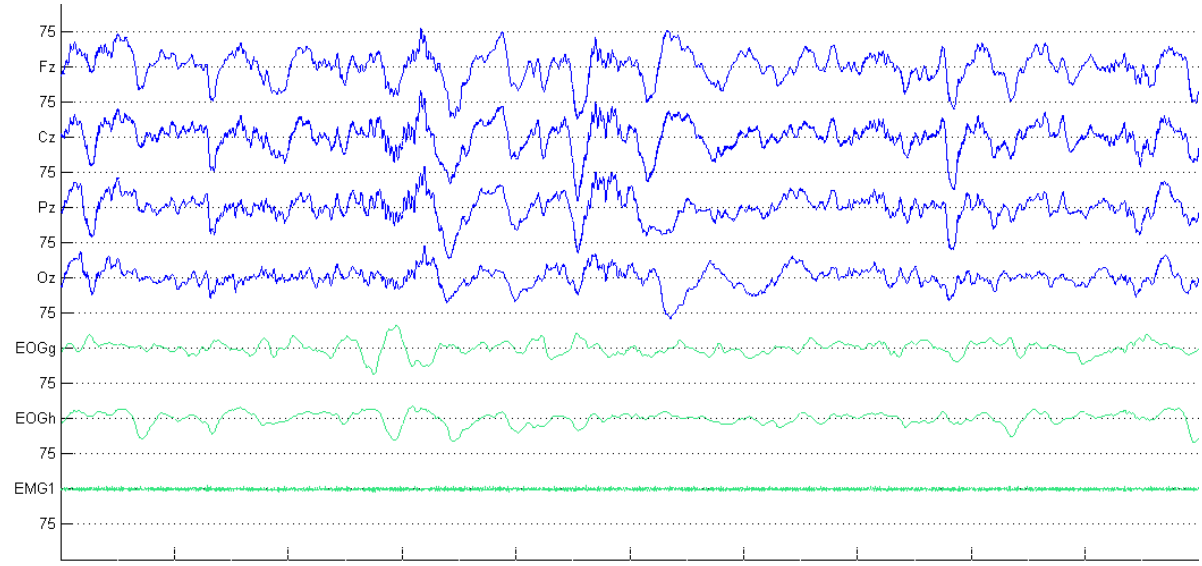


Figure 61. PSG during SWS . Slow delta waves dominate the EEG pattern, with an overshoot in the EOG. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

## REM sleep

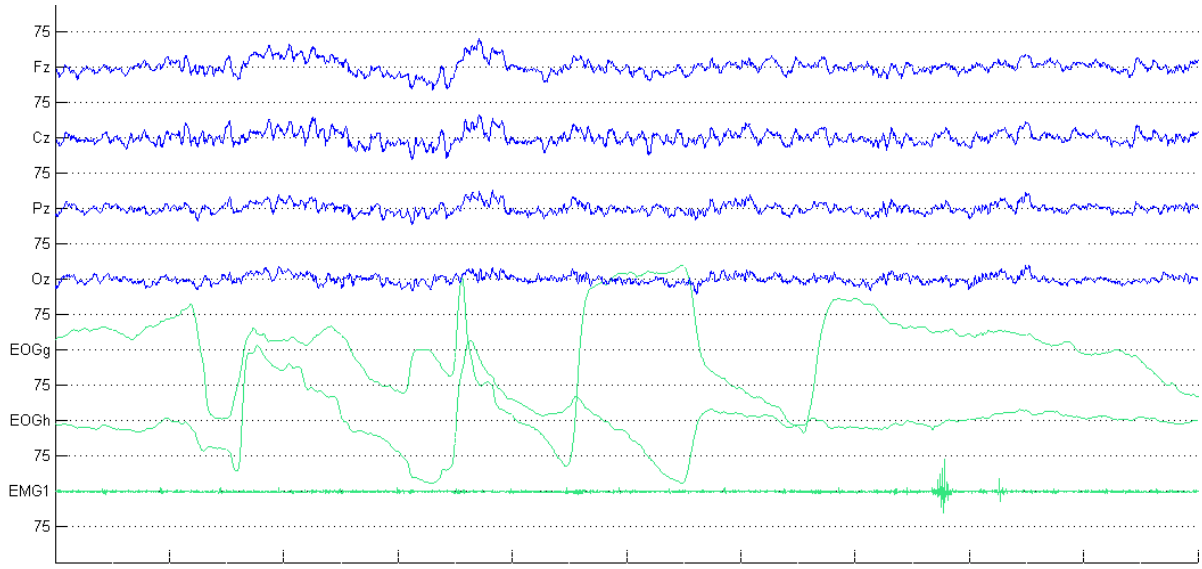


Figure 62. PSG during REM sleep, showing brusque, rapid eye movements and a mixed, low voltage EEG pattern. (Recordings from high to low: blue EEG electrodes Fz, Cz, Pz and Oz, green horizontal and vertical EOG, and green chin EMG)

## 6.2. Examples Tetris reports

This section contains examples of the sleep-onset reports of our first study. On each awaking, volunteers were instructed to report their level of sleepiness according to the Karolinska sleepiness scale (a subjective scale between 1 and 9) and any "thoughts, images, feelings, sensations or anything else going through their mind".

Reports which began with a delay of more than 30 seconds after the auditory stimulus, reports which could not be completely transcribed, and moments when the subject did not respond at all, were not used in analyses.

### 6.2.1. Tetris-related content

Images of Tetris included all reports where the subject explicitly mentioned seeing the Tetris game. One subject said*: "Level five. And euh I've been thinking about Tetris, about the green blocks, and euh it's difficult to put them in the right place."* Another subject had hypnagogic hallucinations about other versions of Tetris he made up in his mind*: "Level eight… I've been thinking at Tetris, but euhm I'm seeing it horizontally… In fact, with blocks arriving at the right, and I have to complete vertical lines."* Another example of another version: *"Level seven… and I was thinking about the music of Tetris, and also about a faster version in which the blocks are falling faster… That's it."*

Images of spatial arrangement and movements which are perceived as ordering Tetris blocks include all kinds of objects such as boxes, bottles, cars, circles, crosses, beds, curtains, beehives with honeycombs, pieces of wood, snakes, eggs, balls, snow, etc*. "Euhm… seven, and I was ordering lots of beds, and putting the sheets on the beds and stuff like that. I was playing Tetris with the beds." "Euhm seven. Otherwise I was ordering everything that is in my wardrobe. I have put everything in shoe boxes, but in my dream there were other shoe boxes. […] In my dream the shoe boxes were of different colors." "Five, and I was seeing a lot of snakes, but with structure in it. Quite weird… Tetris style structure, really weird." "I was dreaming about bees and their beehive, the place in which the bees live. In fact, it was not really the beehive, but especially the honeycombs inside the beehive. That made me think about the forms of the Tetris blocks." "Euh level of sleepiness five. I was seeing myself in euh… nearby a tree trunk, I was busy cutting pieces of wood, which didn't have the same form euh. That's it. […] Then, I don't know why, but the moment when I was seeing myself cutting pieces of wood, I was thinking about Tetris." "Euh eight. And I was still seeing little luminous circles of different colors interweaving. […] Little circles who were interweaving like this, tjoep tjoep tjoep. Little circles, little discs. And they had, they had the same colors as the blocks."*

Unimodal reports containing the sound of Tetris are for example those containing the Tetris song without other mental representations: *"Level four euh… I've still been thinking about the Tetris music and euh… That's it, yes."*

More often, reports containing the melody of the Tetris theme were multimodal. *"Hm… between seven and eight. And I was opening and closing the rolling shutters, on the melody of Tetris." "I had the music of Tetris in my mind, but at the same time I was thinking about other things with the music as background." "Level eight. Euh… I was thinking about the music of Tetris. And I was imagining there were people dancing on that music, people I didn't recognize."*

Other melodies related to the Tetris theme were, for example, other themes of the Tetris game which were not heard during the practice sessions, other Russian folk songs, or songs of which the subject explicitly says they are induced by the Tetris theme. *"Euh seven… and… and I was in a waiting cue for a concert and I was hearing the music 'Nous aimons vivre au fond des bois'. […] It's a song I have been singing when I was young, euhm in the youth movement, and I think it's the same music like the Tetris game in fact. But, but it's instrumental music in fact, you should check it. The Tetris melody has its origin somewhere, and I think it is derived from that song, but you should check it."* It should be noted that both the Tetris melody and the song 'Nous aimons vivre au fond des bois' are Russian folk songs, and their melodies are quite similar. *"Seven and that song (Tetris) was irritating me. Therefore I started thinking at another song, that of Pocahontas, I suppose at the waterfall with the boat… and that euh… raccoon. […] I have been thinking at the melody of Tetris, lalala, and then it started to annoy and then I switched to that other song."*

Plain thoughts of the Tetris game are for example thoughts about the high score. *"Level six. I've been thinking about the scores I have achieved at Tetris and euh… that's all at this moment." "Level five… and I've been thinking about the maximum score I've achieved, euh… and also about the red descending blocks, that's all."*

Emotions related to the Tetris game included excitement, curiosity, happiness, boredom, frustration and disappointment. *"Multiple short dreams like that, and euh I've seen myself playing Tetris. It was a moment when I lost a game and that was frustrating me!" "Yes and in the beginning I would say it was very funny! It was completely dark, and there were several purple and red Tetris blocks or Duplo blocks. In fact it was 3D, and they like tjoep tjoep, formed a little path, tjoep tjoep tjoep. It was very cute!" "That one with four blocks, that orange one. You always need the tail, the long tail of that block euh, and you have to fit that tail in the other blocks. And always when you need a block in one direction, you get a block in the different direction. That's very irritating."*

Images, sounds, thoughts or emotions of another game included reports about video games (for example pac-man), TV games (for example word games and quizzes) and party games (for example chess, downfall, connect four, battleship, card games, dice, pétanque, poker, monopoly, etc.). *"Nine, and I was thinking about a horse of chess." "Level six. I was thinking about Tetris, and I was also thinking about a game "Downfall", where you have to turn and align four disks of the same color." "I've been thinking about*

*another game, more or less the same… It's not really the same objective, it's more or less the colors of Tetris." "Seven… level of sleepiness seven. And euh I have been thinking about a video game." "I was thinking about a game I know, and that made me think of Tetris, I suppose. Pac-man two."*

Images, sounds, thoughts or emotions related to the experimental settings, one of the experimental tasks or questionnaires, sleep related concerns include all reports about the PVT, scales, sleeping or sleep stages, beds, clocks, monitoring, actimetry, questionnaires, the experimental room, the laboratory, the experimenter, the announcement of the experiment, signing the informed consent, etc. *"Eight. I was thinking that it's very annoying, being awoken when you fall asleep." "Seven euh… something about nine o'clock but I don't remember."* Also the laboratory and the university campus occurred in the reports: *"Seven and euhm… I was at the Cyclotron, which wasn't here at Sart Tilman, but which was at the Place de Vingt Août." "I think… in fact, I think I was dreaming I was awoken and I had to answer your questions." "Euh six and a half, and I was imagining taking a nap." "Seven, and I was thinking about, just at the different stages of sleep… one two three four five six seven." "Euh still five or six, and I believe that I thought about… about this experience, with the electrodes." "Euh level four. And euh… I think I was filling out a questionnaire, maybe there was someone with me. I don't remember what the questionnaire was about. It was a questionnaire on sheets of paper." "I, I believe I was looking at a poster. I was wondering if it was a poster which, which showed the different levels of sleepiness. That would be funny." "Euh seven. Euh a male who's looking for volunteers for studies at the Cyclotron." "Level eight. And euhm. A blurred image about someone who talks about his sleep."*

As hypnagogic hallucinations tend to disappear immediately when they are concentrated on, subjects often forgot their mental content. Sometimes they just mentioned the KSS score, said they had nothing going on in their mind, or mentioned they forgot. *"Euh six and euh… pff I don't know euh, yes, I'm feeling tired." "Euh I don't know, six. And it's really very blurred, I don't know anymore." "Level still number nine… Hm."*

The category with other images, sounds, thoughts or emotions not related to Tetris is a very broad one, as it includes all reports which could not be assigned to any of the previous categories. Also, thoughts of other games which were not related to Tetris, when the subject mentioned having played the game recently, were included here. *"Level of sleepiness euhm… seven. And I suppose I was thinking about euh… the poker game of yesterday with a friend." "Seven, eight, and I forgot what I was thinking about… Something related to the university, I think." "Eight. I was thinking about the citytrip I've made with my girlfriend to Paris, about ten days ago." "Level six. Euh I was thinking about what I'm going, euh what I'm going to do during the weekend."*

### 6.2.2. Sensory classes

Visual hypnagogic hallucinations included for example: *"Level of sleepiness seven… and I was thinking about a landscape of the sea, that I was looking at." "Seven, and euh an image of a, a road, with cars." "Sleepiness seven, and I was ordering the bottles with herbs and oils, in the cupboard, at home." "My level of sleepiness is four, and I had an image in my mind with euh lots of people, some people I know, others I don't recognize. And euh they were having a party. I had the impression that I was watching the party."*

Auditory hypnagogic images included all reports were the subject mentions hearing a sound. *"Level six… and I was thinking about the music of the Tetris game, and I was thinking also about a computer game I have been playing ten years ago." "Euhm seven… and my alarm clock went off but if was not at the same place in my room like usual." "Euhm six and a half… in the streets was music, which was very loud and very fast, and people were marching very fast." "Level eight. And euh I had a song in my mind, a song I have been listening to this morning when I woke up."*

Plain thoughts included for example: *"Six or seven. I was thinking… what I should buy when I'm going to live on my own. Little things like… detergent, soap, like that." "Level five. No precise sensations… euh I, I am thinking what I'm going to do euh next week."*

Bodily feelings and kinesthetic content, which is related to the position of the body, weight, movements of the muscles, tendons and joints are categorized together. *"Euh seven… I would wake up anyway, because I was falling." "Euhm my level of sleepiness is four. I've had a strange sensation… It was about making a movement, but I don't know if I really made the movement. It was a movement that I wanted to make, and in the mean time I wanted to stop it." "Level eight… I had the impression that my arms were slightly moving." "Euh I'm cold… yes I'm very cold, I don't know why. It's okay." "Level eight. I've had some shivers… and euh I imagined the Tetris blocks like they were animals."*

Emotions were not a common type of content during this experiment. However, some reports contained emotions: *"Between seven and eight… I'm very startled by your voice. I don't remember what I was thinking about, but I do remember the sound of… of the music of Tetris." "Euhm my level of sleepiness… four. I've seen something euh, in fact I felt very angry or something like that." "Eight. And I'm scared."*

## 6.3. Curriculum vitae

Caroline Kussé

Personal info

Hoogstraat 242/2, 2570 Duffel, Belgium
Tel 0032 478 259 111
Caroline.Kusse@gmail.com

Born 18/02/1986
Married
1 Daughter

Education

**PhD neurosciences** 2009-2014
University of Liège, FRIA grant
Thesis: Functional interactions between memory processes and spontaneous brain activity: behavioral, EEG and fMRI studies

**Master biomedical sciences, neurosciences** (magna cum laude) 2007-2009
University of Antwerp - University of Liège via Erasmus Belgica
Thesis: Activity-dependent induction of hypnagogic images during naps: a pilot behavioural study, Cyclotron research center
Stage: Laboratory of cell biology and histology

**Bachelor biomedical sciences** 2004-2007
University of Antwerp
Thesis: Correlation between the sleep/wake rhythm and electrical coupling by the gap junction protein connexin36 in retina, nucleus suprachiasmaticus and glandula pinealis (literature review in Dutch)

**Secondary school: Latin and mathematics** 1998-2004
Koninklijk Lyceum Antwerpen

## Working experience as jobstudent

| | |
|---|---|
| Research, CRC, University of Liège | September 2009 |
| Library clerk, University of Antwerp | May 2005 – June 2009 |
| Moving library collection, University of Antwerp | October 2007 – March 2008 |
| Cashier, GB Schilde | July 2005 & 2006 |
| Babysitting, Goyvaerts Zoersel | July 2002 & 2003 |

## Skills

Functional neuroimaging
- EEG & signal processing
- fMRI & image analysis
- Histological preparation of sections & examining with light-, electron- and confocal laser scanning microscopy

Computer knowledge
- Matlab, Cogent: basics
- SPM, DCM, FASST: very good
- MS office: word, powerpoint, excel: very good
- SPSS: moderate
- Photoshop: basics

Language knowledge
- Dutch: native language
- English: fluent written scientific literature, good everyday language
- French: good written and spoken language

Driver's licence B

First aid basics, Rode Kruis Vlaanderen

## Hobbies

Gym group workouts
Judo
Outside walking, running and cycling
Playing classical piano

## Research experience

Tetris 2008-2011

Hypnagogic hallucinations are conscious mental representations that emerge spontaneously at sleep onset. We found that task-related hypnagogic hallucinations during a daytime nap were more consistently induced by experience than by anticipation, incorporating the same modalities of the task.

Techniques: questionnaires, polysomnography (basic EEG, EOG, EMG), sleep scoring in FASST, SPM, Matlab, SPSS

Sponmem 1 2009-2014

Memory consolidation is thought to depend on the reactivation of patterns of brain activity that characterize recent experience. Using multivoxel pattern analysis, we found that patterns of task-related brain activity in the ventral visual stream persist into immediate rest periods and that this persistence seems to be related to memory performance, suggesting that replay of brain activity contributes to memory processing. However, other analyzing techniques could not confirm these findings.

Techniques: questionnaires, fMRI, sMRI, Cogent, Matlab, SPM, DCM for fMRI, SPSS

Sponmem 2 2011-onwards

Idem

Techniques: questionnaires, EGI (high density EEG), sMRI, Cogent, Matlab

PER 3 2010-2011

Interindividual differences in sleep-wake regulation are associated with a polymorphism in the gene PERIOD3: people homozygous for the longer allele (PER3 5/5) generate more slow wave activity during NREM sleep and theta activity during wakefulness and are morning types, relative to individuals with the shorter allele (PER3 4/4) who are evening types. We found that PER3 5/5 individuals are more vulnerable to sleep loss in the period just before the wake maintenance zone, under 42h of sustained wakefulness.

Techniques: behavioral tasks, EEG during constant routine, fMRI, sMRI

DCM sleep 2010-2012

The fundamental rhythm of human NREM sleep is the slow wave activity, large amplitude delta waves between 1 and 4 Hz. We used DCM to investigate changes in effective connectivity in default mode network areas involved in the generation of slow wave activity. We found that the increased cortico-cortical synchronization during NREM sleep is mediated through cortico-thalamo-cortical interactions rather than through a substantial change in long-distance cortico-cortical connections.

Techniques: DCM for EEG, SPM, Matlab

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- Schrouff* J, *Kussé* C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding semi-constrained brain activity from FMRI using support vector machines and gaussian processes. PLoS One 7(4): e35860.

- Schrouff J, *Kussé C*, Wehenkel L, Maquet P, Phillips C (2012) Decoding spontaneous brain activity from fMRI using gaussian processes: tracking brain reactivation. In: PRNI, London, doi 10.1109/PRNI.2012.19.

- Schrouff* J, *Kussé* C*, Wehenkel L, Luxen A, Maquet P, Phillips C (Submitted) Temporally structured memory replay during resting wakefulness in humans.

- *Kussé C*, Schrouff J, Phillips C, Maquet P (In progress) Dynamic causal modeling reveals temporally structured memory replay during resting wakefulness in humans.

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- Jedidi Z, Rikir E, Muto V, Mascetti L, *Kussé C*, Foret A, Shaffii-Le Bourdiec A, Vandewalle G, Maquet P (2011) Functional neuroimaging of the reciprocal influences between sleep and wakefulness. Pflugers Arch 463(1): 103-109.

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- Schrouff J, *Kussé C*, Wehenkel L, Maquet P, Phillips C: Decoding spontaneous brain activity from fMRI using Gaussian Processes: tracking brain reactivation. Talk at PRNI, London, UK, July 2-4th 2012

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